# The American Journal of Surgery

EDITED BY THURSTON SCOTT WELTON, M.D.

December 1943

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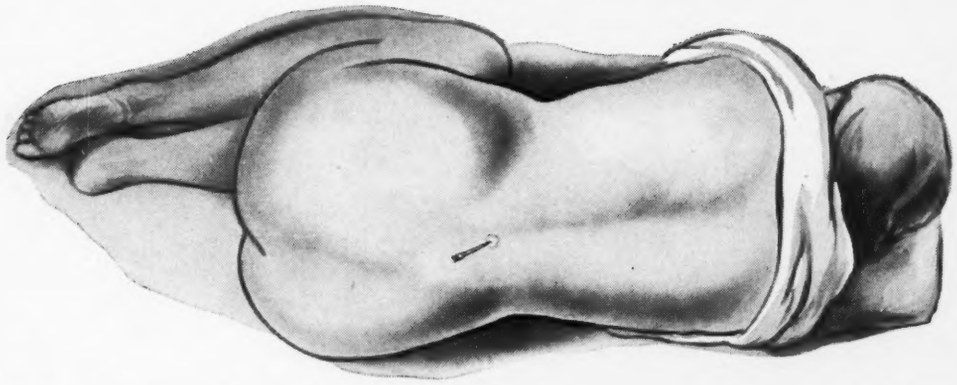

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*Kubic, C. S., and Hampton, A. O.: Removal of Iodized Oil by Lumbar Puncture, New England J. Med. *224*:455 (Mar. 13) 1941.

‡Klemme, R. M., Scott, W., and Woolsey, R. D.: Intraspinal Protrusion of Intervertebral Disks: Observations on Diagnosis, J. Missouri M. A. *39*:131 (May) 1942.

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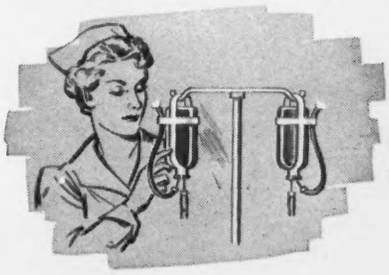

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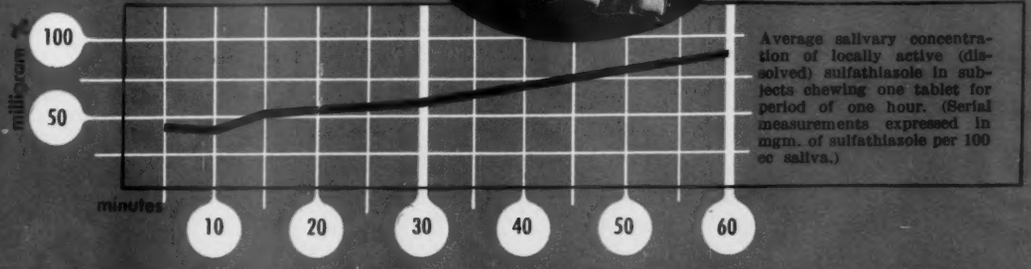


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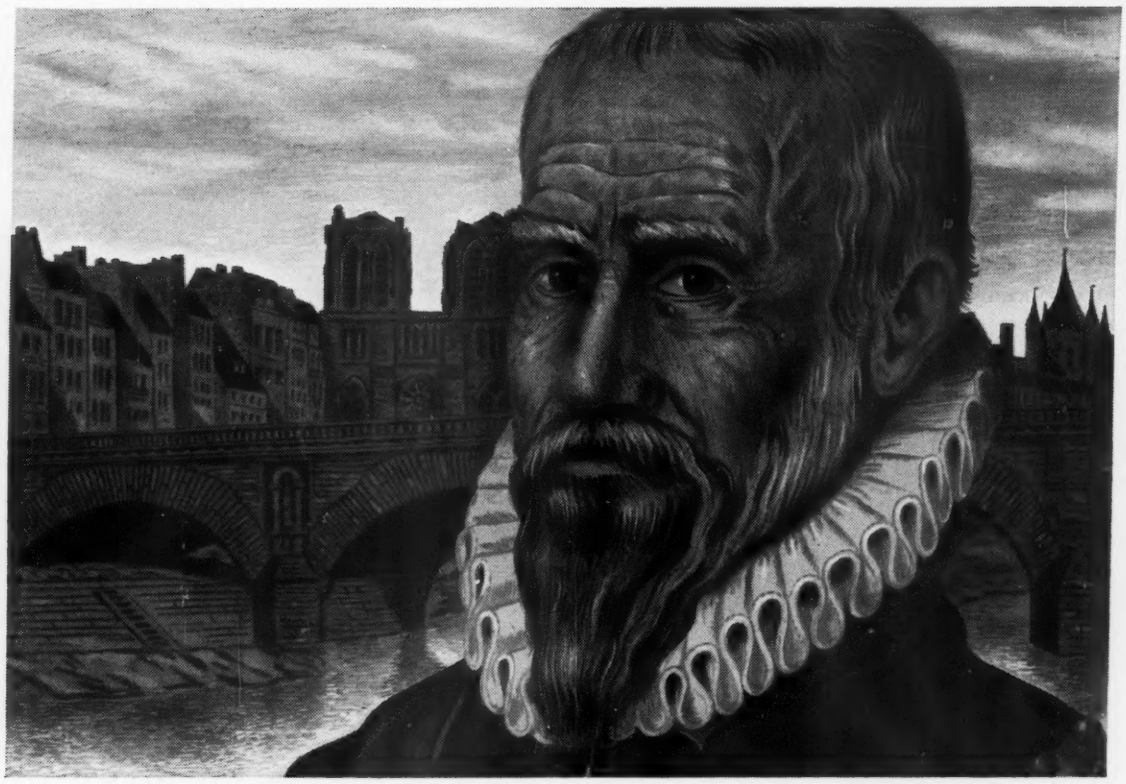

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| 5. Non-mercurial II, tincture | 1:13,000 | 1:40,000 |
| 6. Non-mercurial II, solution | 1:7,000 | 1:30,000 |
| 7. Mercurial I, tincture | 1:4,000 | 1:26,000 |
| 8. Iodine, tincture | 1:2,000 | 1:20,000 |
| 9. Iodine, aqueous | 1:1,000 | 1:18,000 |
| 10. Mercurial II | 1:3,000 | 1:10,000 |
| 11. Mercurial III | 1:1,500 | 1:10,000 |
| 12. Non-mercurial III | 1:3,000 | 1:8,000 |
| 13. Mercurial IV, solution | 1:1,500 | 1:8,000 |
| 14. Mercurial IV, tincture | 1:2,000 | 1:5,000 |
| 15. Mercurial V, tincture | 1:2,000 | 1:3,000 |
| 16. Chloramine T (U.S.P.) | 1:250 | 1:2,000 |
| 17. Mercurial V, solution | 1:300 | 1:1,000 |
| 18. Non-mercurial IV | 1:100 | 1:950 |
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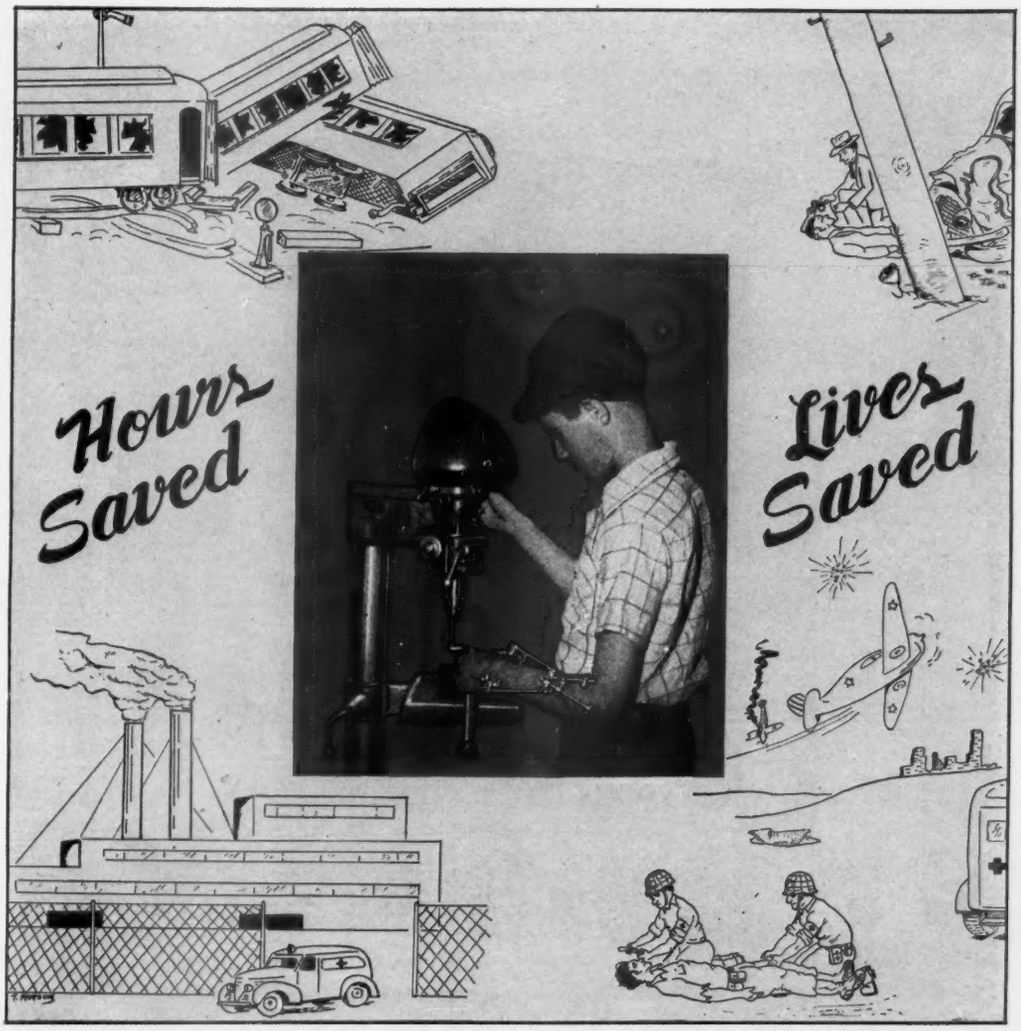


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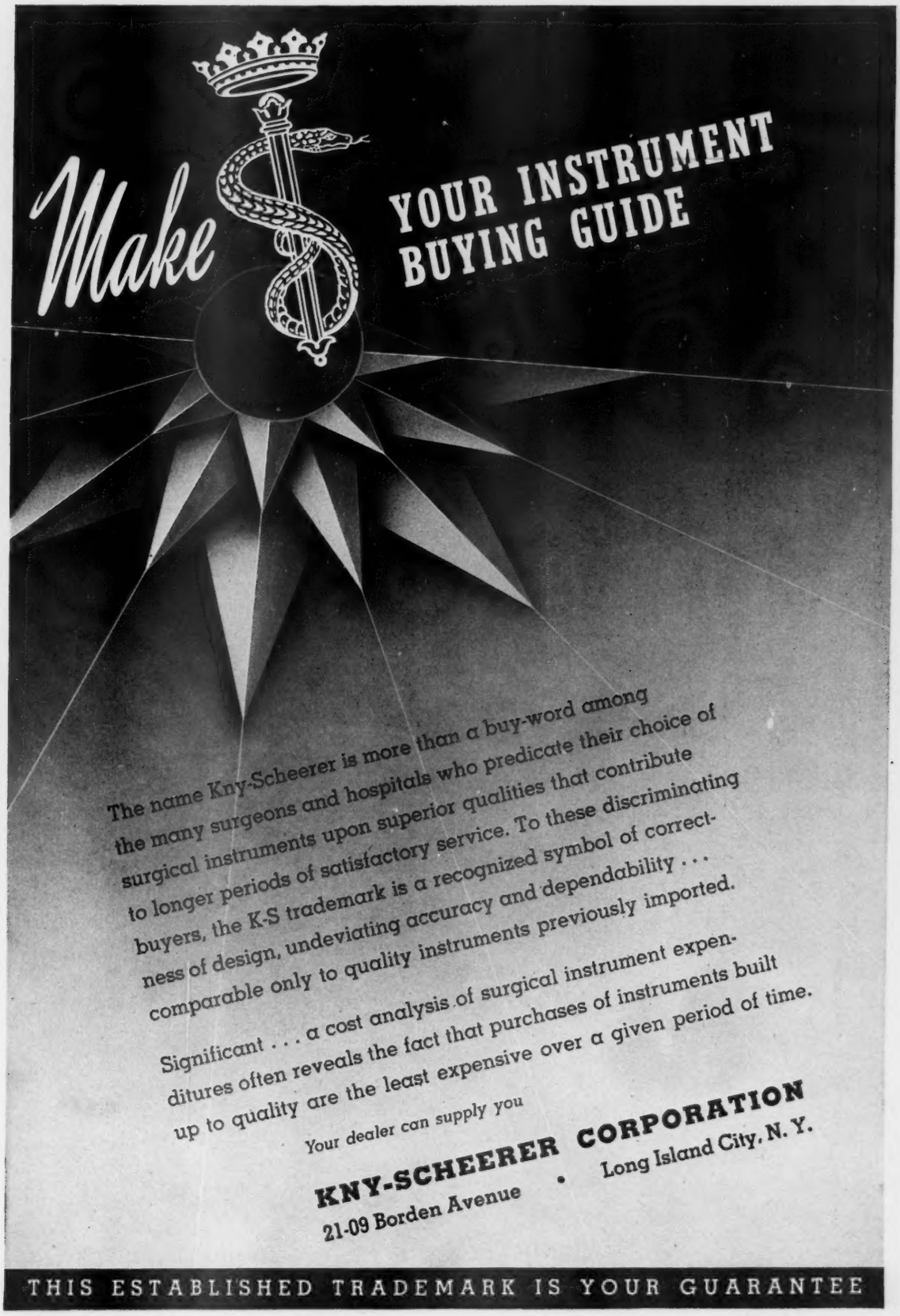
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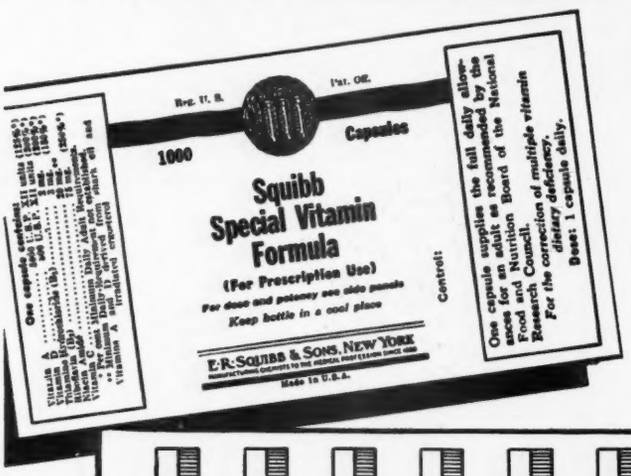
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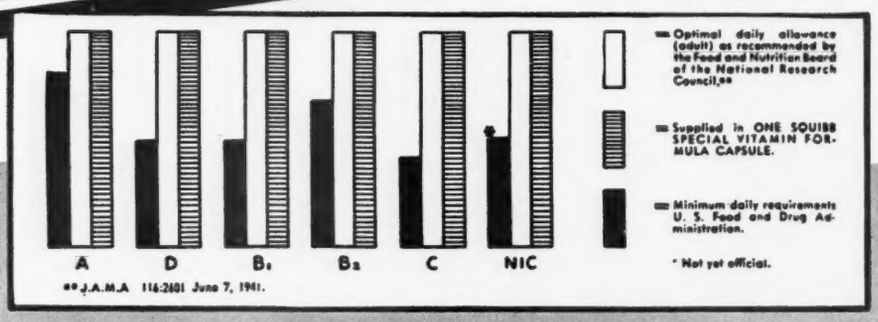
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** J.A.M.A. 116:2601 June 7, 1941.

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(1) Spies, T. D.: *J. A. M. A.* 122:911, July 31, 1943.
(2) Jolliffe, N., and Smith, James J.: *M. Clin. North America* 27:587, March 1943.

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NO. VI

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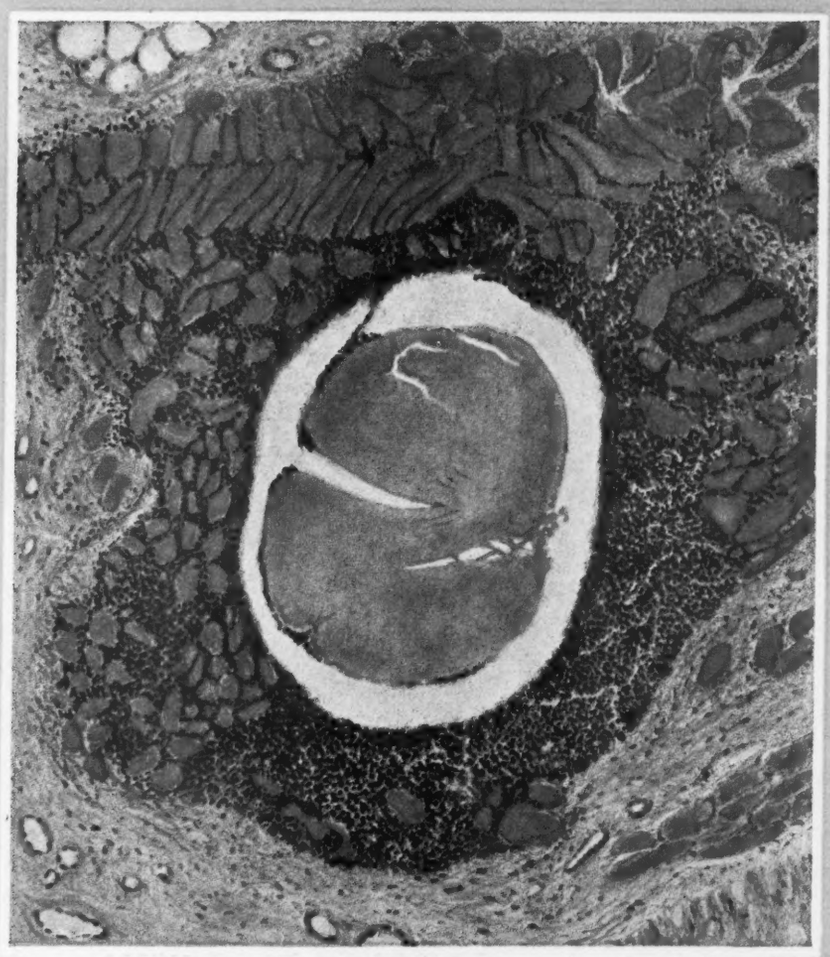
This development is based upon research which has demonstrated that the degree of tissue reaction to gut is directly proportional to the size of the suture. When fine gut is used there is less tissue trauma from the suture itself and from its transit; correct apposition is facilitated. The possibility of dead space is decreased.

These factors, in combination with the accepted surgical axiom that the tensile strength of any suture need never exceed the tensile strength of the tissues it holds, are responsible for the utilization of finer gauged sutures.

The accompanying drawings from histologic sections illustrate tissue reaction to surgical gut.



**1.** Composite section showing Size 2 Medium Chromic Surgical Gut imbedded in abdominal wall of a rabbit. Tissue was excised on seventh postoperative day. (Hematoxylin and Eosin stain.) Magnification of drawing, x50. Note extensive leukocytic infiltration and inflammatory exudate. Clear zone surrounding surgical gut is due to fixation shrinkage.

**2.** Composite section (x50) showing Size 00 Medium Chromic Surgical Gut imbedded in abdominal wall of rabbit, and removed on seventh day. Note minimal leukocytic infiltration and absence of inflammatory exudate in marked contrast to extensive reaction with larger suture. Clear zone surrounding surgical gut is artifact due to fixation shrinkage.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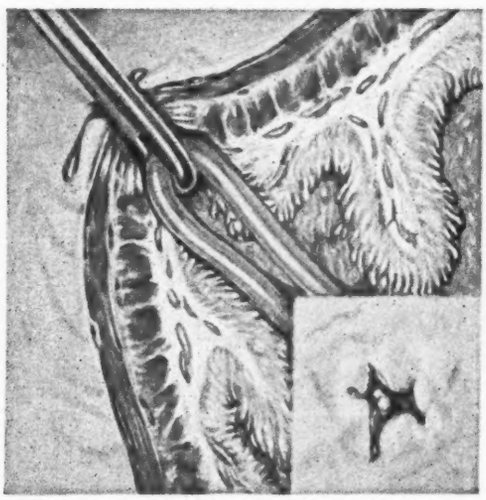

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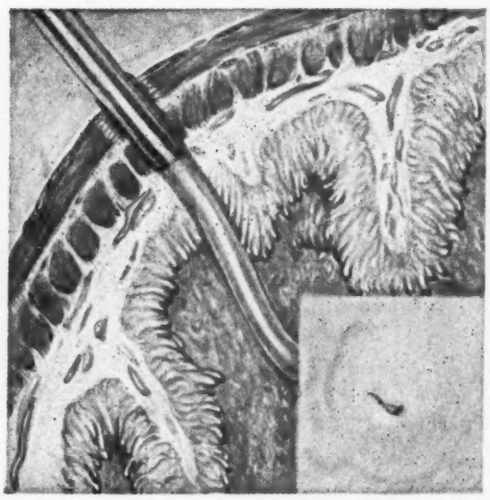
The eyed needle does greater injury to tissue because it pulls a looped suture in its wake.



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NEW SERIES VOL. LXII DECEMBER, 1943 NUMBER THREE

# Editorials

## THORACIC SURGERY AFTER WORLD WARS I AND II

IT has become more or less axiomatic that surgery of the chest came out of the first World War. Many presume that thoracic surgery will become perfected in World War II.

In these days of catastrophic and rapidly changing events it might appear inappropriate to attempt to predict the status of thoracic surgery after this present war. And it might appear on first thought that there is little to be achieved by such an attempt. Retrospective consideration, however, of the development of surgery of the chest after World War I may indicate that there is something to be gained by evaluating the reasons and trends which have brought about this development. The average physician and surgeon might better acquaint himself with his place or responsibility in the future development of chest problems by such an evaluation.

*Until the possibilities of a science become somewhat generally appreciated by scientists,* that science cannot be said to have reached even an adolescent stage. It might be stated that thoracic surgery began its adolescence when Evarts Graham and his co-workers proved during the influenza epidemic of the last war that mediastinal flutter was being produced by surgeons who were resecting segments of ribs before postpneumonic thin pleural effusions had become purulent. This demonstration directed the minds of most of the profession to a chest problem which confronted them frequently in civilian practice. And, furthermore, it gave them tangible knowledge *within their own province of therapeusis,* a worth while therapeutic principle most of them could apply themselves if need be. As a consequence, the general profession came to realize that thoracic surgery perhaps could have a wider practical application than they had suspected previously.

If the value of a medical science is in direct proportion to the number of the profession who are able to apply its possibilities in a diagnostic and therapeutic way, it is easy to understand and explain why thoracic surgery has a long way to go before it reaches its maturity, a state of maturity comparable to that of abdominal surgery. Brunn's consecutively successful lobectomies for bronchiectasis (a procedure which previously had been essentially discarded because of the high mortality rate attending it) reported in 1928, Evarts Graham's magnificent accomplishment of total pneumonectomy for carcinoma of the lung in 1933 which will stand as a golden milestone of achievement, Garlock's original report of three consecutively successful resections of the mid-portion of esophagus for carcinoma, contributions to the surgery for tuber-

culosis, these and accomplishments by other distinguished men whose names will live indefinitely but of whom space will not permit mention here, fired the imagination and the enthusiasm of many and resulted in a tidal wave of dramatic accomplishment in the chest field during the past fifteen years. But so far, the execution of major, thoracic, surgical procedures has been beyond the surgical environment of many men. Well co-ordinated teams, including those especially trained in anesthesia, in the technic of bronchoscopic aspiration and postoperative inhalation therapy, are necessary for most major intrathoracic procedures. Such teams have not been nor will they be available to the majority for some time to come.

The average surgeon, pressed as he is by everyday problems, has not only found the performance of thoracic surgery beyond his scope, but has failed to inform himself and become sufficiently conscious of the early signs and symptoms of many surgical disorders of the chest. Most men have failed to realize that their own vista of usefullness in the field of early diagnosis and treatment of even less difficult and more frequently occurring surgical chest problems than carcinoma of esophagus or bronchus, has been widened markedly. The present great need in the profession as a whole is for correction of this latter phase of the problem.

During the present war those younger surgeons who serve in the battle zones especially, will become inculcated with knowledge and experience pertaining to wounds of the chest. Only a very limited number of surgeons situated in certain centers will have the opportunity to deal extensively with varied thoracic surgical disorders. But nevertheless many will return from the war, conscious that certain problems of chest surgery belong within their own therapeutic domain even under ordinary environmental conditions.

In the first two decades which will follow this war, surgeons who previously would not have attempted surgery for lung abscess will resect segments of the ribs for this disorder under local anesthesia, doing a one-stage operation (according to localization principles of Neuhof and Touroff) as easily and effectively as they have previously resected a segment of rib for empyema. Fewer patients will die from tension pneumothorax after an automobile accident with a mistaken diagnosis of "shock." He who neglects an acute postpneumonic empyema will be labeled, as he is to some extent now, as a charlatan or an ignoramus. And sufficient stimulus will arise to develop gradually the realization of the general profession to its diagnostic responsibility.

The general profession will begin to appreciate that it does not suffice for one to make a diagnosis of lung abscess or empyema, that the causes of these disorders are varied and the etiologic agent should be specified in the diagnosis if possible; that, for example, carcinoma of the lung may be the etiologic agent in both; that the bacteriology in lung abscess and in empyema varies and may make considerable difference in therapeutic indications; that our conceptions of therapy for tuberculous, straw-colored effusions have changed in recent years, (that such effusions are no longer left in the pleural cavity indefinitely upon the theory that they should be so left to keep the lung at rest); and that "unresolved pneumonia" is an almost obsolete term being replaced by more specific reference to etiology and pathology.

Though some surgeons in this war may see more blood in a month than they have ever seen before, or suture a thousand wounds a month, the problems of disease, of malignancy, of trauma, will remain closely interwoven with the complexities of anatomy, physiology, bacteriology, chemistry, and pathology. And those who master the diagnosis or therapeusis of thoracic problems must of necessity think in terms of these great sciences. The war surgeon of today who thinks in this manner as he performs his surgery can do much

to stimulate the profession at home tomorrow where stimulus is most needed.

Surgery of the chest has probably outgrown a stage at which a single discovery, as that of the U. S. Empyema Commission of the last war, can so profoundly affect its development. Surgery of the chest will reach its maturity as the general profession fashions its methods of thought regarding chest problems on a pattern of fundamental sciences in a diagnostic way, as it now does regarding the diagnostic problems pertaining to abdominal surgery.

J. K. DONALDSON, M.D.

## PLASTIC SURGERY IN THE ARMY*

IN reply to an article which I read before the American Society of Plastic and Reconstructive Surgery in December, 1942, and which *The American Journal of Surgery* quoted editorially in its issue of September, 1943, Major General Norman T. Kirk, Surgeon General of the United States Army, complains that the implications of my article are "absolutely unfounded and unjustifiably animadversional." He further intimates that insufficient effort was made by me to ascertain the true situation. In view of this criticism I am constrained to present the following facts:

1. My paper, as stated above, was presented at the annual meeting of the American Society of Plastic and Reconstructive Surgery in December, 1942. The advances in the organization of the Army's program for plastic surgery, which the Surgeon General cites, were inaugurated according to his own statement, "many months ago."

2. Before preparing this article, I wrote to the Office of the Surgeon General for information on the then-status of plastic surgery in the Army. The reply dated September 25, 1942, stated that "It will be impossible for this office to collect any data on the present status of Plastic and Reconstructive Surgery in the Armed Forces at this time" and referred me to the Sub-Committee on Plastic and Reconstructive Surgery of the National Research Council. I pursued the suggested avenue of inquiry without success. In fact, in February, 1943, I was authoritatively informed that this committee had no information as to the fate of its suggestions to the Surgeon General's Office.

3. In June, 1943, three months before the editorial in question was published, a copy was sent to the Office of the Surgeon General. I received an acknowledgment dated June 14, 1943, which in no way questioned the accuracy of my statements or suggested any corrections therein.

Since my sole interest in this problem is the proper organization of military facilities for plastic surgery, I am gratified by the outline of such facilities by the Surgeon General. I am citing the above facts merely to show that I did make every effort to ascertain the true status of the Army's organization for plastic surgery and that the Office of the Surgeon General had full opportunity to make any corrections they desired before publication of the editorial.

JACQUES W. MALINIAC, M.D.

* The editor is not responsible for the views expressed by the authors of articles appearing in the Journal. It has been the custom when some one wrote the editor criticizing or commenting on material in the Journal for the letter to be sent to the author of the article for his personal reply and comment. In the above instance we violated this rule and published Major General Kirk's criticism. Therefore, in all fairness, we are publishing Dr. Maliniac's reply. As far as we are concerned, this closes the issue.

# Original Articles

## PROGRESS IN THE MANAGEMENT OF HEMORRHOIDS

EDWARD T. WHITNEY, M.D.
Surgeon-in-charge, Rectal Clinic,
Boston Dispensary

AND

GASPAR ANGELO, M.D.*
Assistant Surgeon, Rectal Clinic,
Boston Dispensary

BOSTON, MASSACHUSETTS

MUCH progress has been made in the treatment of hemorrhoids since suppositories and the clamp and cautery were the sole forms of therapy. In fact, we now know that suppositories are practically worthless except, possibly, as a palliative measure and the treasured pearl-handled cautery clamp gathers dust in the usual hospital display of antique instruments. And yet, there is a surprising amount of confusion among the medical profession as to just what hemorrhoids are and as to how they should be handled.

### A PLEXUS OF VARICOSITIES BENEATH REDUNDANT MUCOUS MEMBRANE

A hemorrhoid is a redundant pouch of rectal mucous membrane or anal skin containing a plexus of varicose venules. Early recognition of the fact that it is a plexus of very small varicosities and not one large vein will banish some of the confusion. Furthermore, an understanding of the genesis of such a condition will also help but this requires a knowledge of certain aspects of the anatomy, physiology and pathological states of the anus and lower rectum.

### THE VEINS INVOLVED

The closure of the anus is accomplished by the tonic contraction of the sphincters which causes the mucous membrane of the much larger rectum to be thrown into a number of folds called the columns of Morgagni. Beneath the mucous membrane of these columns, there is a vast network of venules which collects the blood from this region and delivers it into the portal venous system by way of the superior hemorrhoidal veins. This blood has to be raised approximately a foot from anus to heart and yet no part of the portal venous system is protected by valves.

Furthermore, the superior hemorrhoidal veins lie for the most part within the abdomen on the walls of the rectum but, just above the location of the columns of Morgagni, these veins penetrate these walls to enter the rectum where they then lie just beneath the mucous membrane of the latter. (Fig. 1.) Above this penetration they are protected by the intra-abdominal pressure but below it they, at times, lose this protection as, during defecation, straining at stool and forcible breaking of wind, when this pressure is exerted against all of the contents of the rectum including any redundant mass of varicosities. It is no wonder, therefore, that these little thin-walled veins easily succumb to any factors tending to produce prolonged dilatation and varicosity whether the latter are confined locally to the portal venous system or whether they affect all the more dependent veins of the body.

### GENESIS OF THE VARICOSITIES

Those factors which tend to produce prolonged over-dilatation within the portal

* Statistics in the text referring to the Cambridge Hospital were compiled by Dr. Angelo who is in charge of the Rectal Clinic at the Cambridge Hospital, Cambridge, Mass.

venous system alone accomplish this by increasing the intravenous pressure within that system. This over-dilatation is seen behind an hepatic cirrhosis, behind a cardiac decompensation, in alcoholism, overeating, etc. On the other hand, conditions which tend to produce varicosity generally throughout the more dependent veins of the body, do so by weakening the vein walls so that the latter are unable to withstand the normal intravenous pressure. The latter agents may be either nutritional or endocrine.

Nutritional deficiencies produce both atony of the smooth muscle and atrophy of the connective tissue sheath of the vein wall with ensuing weakness of both. An example of an endocrine influence may be seen in the excessive dilatation of the veins of the legs and anus during pregnancy, a condition which, we believe, is caused by the secretion of the hormone relaxin during this period.[1] This hormone is intended to produce relaxation of the ligamentous, capsular and other connective tissue attachments of the pelvis in order to mobilize the latter somewhat in preparation for delivery. The same effect exerted on the connective tissue structures of the veins would explain the marked increase of varicosities during pregnancy. The end result of any one or combination of these processes is the production of a plexus of varicose venules beneath the mucous membrane of the columns of Morgagni in the lower rectum.

## GENESIS OF THE REDUNDANCY OF THE MUCOUS MEMBRANE

However, another process must occur before this state of varicosity is productive of a hemorrhoid; the mucous membrane and skin overlying these venule varicosities must become redundant. The mucous membrane and skin of the rectum, anus and peri-anum are fixed in various degrees to the latter structures and these fixations have to be stretched or abolished before the mucous membrane and skin can become redundant and form a pouch. The abolition of these fixations is brought about by various forces singly or in combination. The varicosities themselves do considerable dissecting beneath the mucous membrane and the same nutritional and endocrine factors which weaken the vein walls also weaken these fixations and allow the varicose dissection to progress even more easily. Straining of course helps.

## INFLUENCE OF THE CONJOINED LONGITUDINAL MUSCLE

This process of detachment can proceed rapidly beneath the mucous membrane of the rectum and beneath the peri-anal skin but not so rapidly in the region of the anus itself which is the reason why we have several different kinds of hemorrhoids; internal, external, prolapsed, etc. The skin of the anus has inserted into it the conjoined, longitudinal muscle of the bowel wall which fixes it very firmly to the sphincters at the intermuscular septum.[2] (Fig. 1.) This muscle is a continuation and confluence of the longitudinal bands of the large intestine and of the levator ani. It completely surrounds the lower rectum, ensheaths the three portions of the external sphincter and then becomes inserted principally into the skin of the anus at and just below the intermuscular septum.[10] The firm fixation of the anal skin in this region prevents the downward extension of the varicose process which started in the columns of Morgagni so that for some time the process is confined to the rectum and is called an internal hemorrhoid. (Fig. 1.)

However, if the redundancy of the mucous membrane in this region becomes extreme, it may form so large a pouch that the latter can prolapse down through the lumen of the anus thereby producing a prolapsed, internal hemorrhoid.

On the other hand, in some individuals the strands of longitudinal muscle inserted into the skin of the anus can be overstretched[3] by straining and separated by the dissecting action of the venules themselves, thereby allowing extension of the

process into the peri-anal area where once more the skin is loosely attached and once more a redundant pouch is easily produced

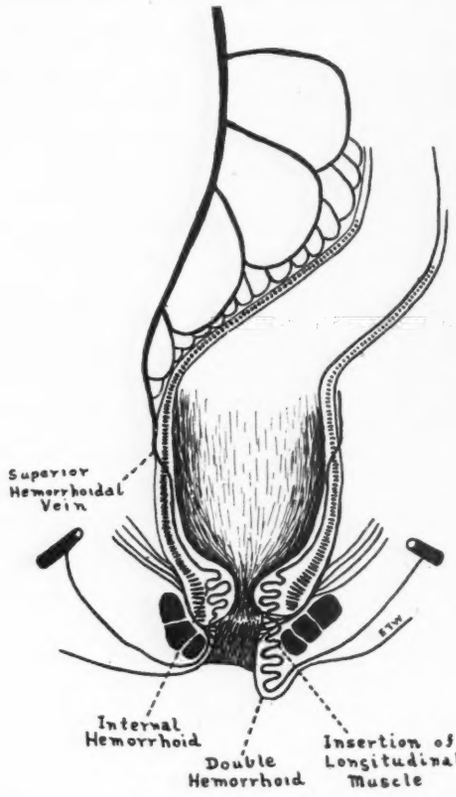


Fig. 1. A diagram illustrating two types of hemorrhoids by means of a sagittal section down through the rectum and anus. On the left is a simple internal hemorrhoid while on the right a double hemorrhoid is depicted. It will be noted that the superior hemorrhoidal vein pierces the rectal wall just above the hemorrhoids to lose its intra-abdominal support and become subject to the strains and stresses of the lower rectum and anus. The insertion of the conjoined longitudinal muscle into the skin of the anus is indicated and it will be seen how this controls the progress of the hemorrhoidal process and consequently governs the type of hemorrhoid produced. On the right, this insertion has been pierced and weakened and the skin has been detached from the anal wall allowing the formation of an external hemorrhoid as well as an internal one.

but this time wholly extra-anal. When this occurs, in addition to the internal hemorrhoid, we have an external hemorrhoid. (Fig. 1.) Such a condition, however, is really a double hemorrhoid as an external hemorrhoid rarely exists without being preceded and produced by an internal hemorrhoid.

Finally, in some individuals, the internal

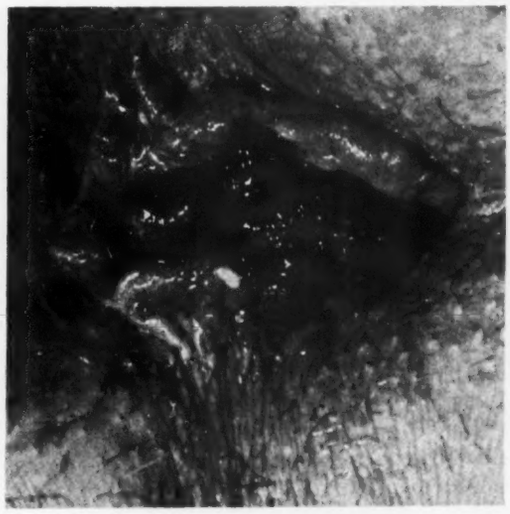

Fig. 2. A prolapsed double hemorrhoid. The dark colored mass in the center is the dusky red, internal hemorrhoid which has intussuscepted down through the anus. This is surrounded by the lighter colored, external hemorrhoids which have really been transformed into fibrotic skin tabs.

part of such a double hemorrhoid becomes so redundant that it also intussuscepts through the lumen of the anus producing a prolapsed, double hemorrhoid. (Figs. 2 and 9.)

There are, therefore, four varieties of hemorrhoids: internal, prolapsed internal, double and prolapsed double. The external thrombotic hemorrhoid (so-called) is seldom a real hemorrhoid. It is nothing more than a thrombosis within some peri-anal venules. It really should be simply called an external thrombosis.

### INJECTIONS VERSUS OPERATION

This much of the pathological process and anatomy must be kept in mind when it comes to selecting the proper method of therapy. The majority of proctologists treat hemorrhoids by both injections and operation depending upon the type of hemorrhoid encountered so that in this article, we shall not consider the other more rarely used methods such as "electrolysis" (galvanism), diathermy, etc. The

question is constantly being asked as to where the line should be drawn between those cases suitable for injection and those requiring surgery. As will be seen subsequently, some definite rules can be made to govern this selection.

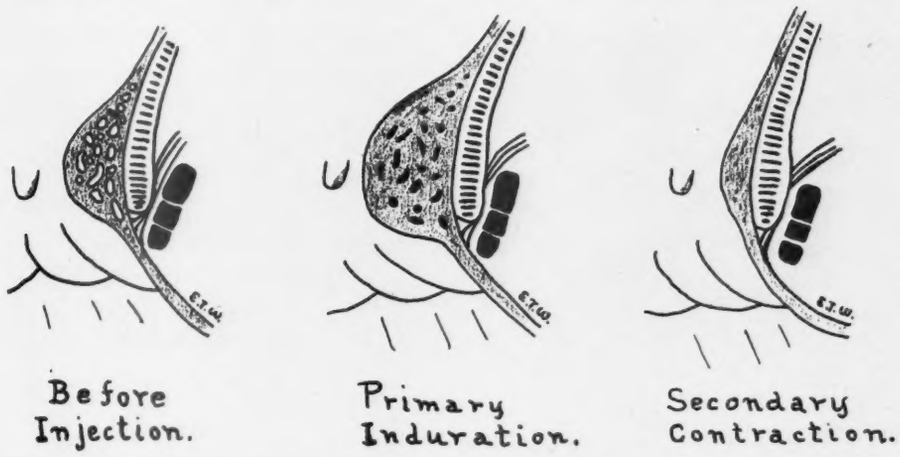


Fig. 3. Diagrams illustrating the effects of an injection on an internal hemorrhoid. The diagram on the left represents a redundant pouch of varicosities prior to injection. The middle one portrays the primary reaction following injection. Sclerosis of the varicosities and induration of the spaces between them has taken place. On the right is shown the end result. The sclerosed veins have been absorbed and the induration has been transformed into fibrosis which has contracted and, in addition to further obliterating the vessels, has reattached the mucous membrane onto the rectal wall.

### MANAGEMENT OF SIMPLE INTERNAL HEMORRHOIDS

Most all simple uncomplicated internal hemorrhoids can be obliterated by injection with suitable chemicals.[4,5,6] How long this obliteration remains or how long other unobliterated veins in the rectum remain free from varicosity varies with the individual. Usually, examination and injection routinely every few years maintains control of the condition.[5]

The injection is made into the internal hemorrhoidal mass or pouch as high up as possible. No attempt is made to put the solution into a vein; the veins are too small for this. Theoretically, there are no nerves of sensation above the mucocutaneous (pectinate) line which is at the level of the internal sphincter about one-fourth inch above the intermuscular septum. Practically, however, it is found that there is some sensation for about one-fourth inch or so above this line. Injection must be made above this demarkation line of sensation otherwise pain and sloughing will occur. From this statement it can be inferred that no injection can be made directly into the external hemorrhoid and, therefore, any attempt to cure the latter by injection must be made via obliteration of the internal hemorrhoid. As this mucocutaneous line is somewhat indistinct at times, we usually advise the novice to ask the patient if he feels the touch of the swab putting antiseptic on the spot where the needle is to be inserted and, if he does, the injection must be made higher up.

Large boggy internal hemorrhoids may have to be injected two or three times[3,4,7] and this should be done systematically, the first injection being introduced into the uppermost pole and subsequently, after the lapse of a suitable time varying with the type of solution used and the amount of contraction obtained, a second or third injection is made lower down or just to either side.

There are two solutions in general use: 5 per cent phenol in vegetable oil and 5 per cent quinine and urea hydrochloride. From 1 to 5 cc. of the phenol in oil and from 1 to

2 cc. of the quinine is the usual dosage. Most proctologists give the other more widely advertised solutions a trial but

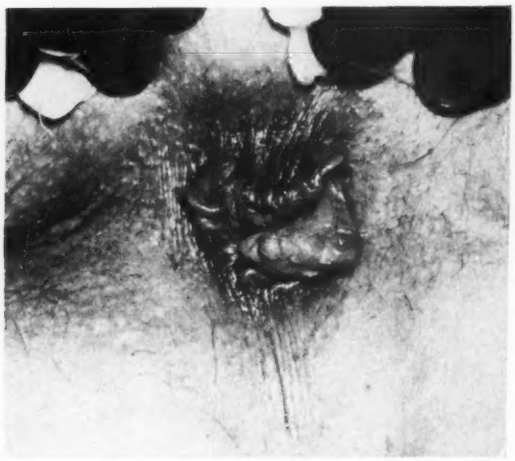

Fig. 4. A photograph illustrating two types of external hemorrhoids. The upper, bluish, patulous hemorrhoid is soft and reducible and would be benefited somewhat (perhaps markedly) by injections. The lower, lighter colored mass is hard and fibrotic, is irreducible and would be affected in no way by injections. However, operation is indicated on both types in the absence of contraindications, as even in the upper hemorrhoid the insertion of the conjoined longitudinal muscle has been irreparably weakened and detached allowing easy recurrence.

something usually turns out to be unsatisfactory. These two solutions have stood the test of time and experience.

Following the injection, there is a primary induration of the tissues beneath the mucous membrane composed of edema and inflammatory cells (mostly round cells). This primary induration can be palpated as a semi-firm lump on the wall of the rectum. (Fig. 3.) With the quinine solution, this lump disappears in a few days or at the most in a couple of weeks but with the phenol it lasts for a month or two which is the reason why we, personally, prefer the former. Sometimes several injections must be made in rapid succession and, if each one produces a lump and if each lump remains in existence for several weeks, the lumen of the rectum soon becomes so surrounded or filled with lumps that evacuation becomes difficult.

Following this primary induration, there occurs a flattening of the hemorrhoid due to fibrous contraction about and obliteration of the varicose venules. (Fig. 3.) Reattachment of the mucous membrane onto the rectal wall will take place if the fibrosis is extensive enough within the hemorrhoid to contact the muscle of the wall. In a large internal hemorrhoid, this does not always occur at first as the first injection produces only a ball of fibrosis in its center which must be fixed to the muscle by one or more subsequent injections. This fact is often overlooked.

### MANAGEMENT OF PROLAPSED, INTERNAL HEMORRHOIDS

Contrary to expectation, a simple, prolapsed, internal hemorrhoid will often completely disappear upon injection especially if it is not too big or not of too long standing. It is surprising to see an angry, secreting, polypoid, prolapsed, internal hemorrhoid disappear within a day or two of an injection of its upper pole. Recurrence in two or three years will often follow however[3,5] but, if the primary fibrosis is made firmly adherent to the rectal wall by repeated injections and, if routine injections are made periodically every year or two, control of the condition can usually be maintained. In case of repeated recurrence or in old, large prolapses, operation is necessary. The latter is almost painless as it simply consists in transfixing the mass as high up as possible and excising it. As this all takes place above the mucocutaneous line where sensation is absent or nearly so, very little discomfort or disability results.

### MANAGEMENT OF DOUBLE HEMORRHOIDS

Often an external hemorrhoid will be improved as the result of injecting the internal one. The fibrous contraction and reattachment following an injection pulls from all directions. Sometimes this is enough to cause a slightly redundant, external hemorrhoid to pull up in. This obliteration, however, may not be perma-

nent and only in early cases will it occur anyway. Remember that this injection does nothing to the overstretched insertion of the longitudinal muscle, so that, dissection of a new varicosity down through the latter is easily and quickly possible. Of course, one might simplify the problem of whether to operate or to inject by insisting upon operation on all double hemorrhoids. However, especially in regards to clinic patients, various reasons are constantly arising for avoiding operation such as contraindications, insufficient money, unavailable time, etc. We, therefore, have formulated the following rule to cover such cases: If the external hemorrhoid is reasonably small, is soft, is reducible and is of a normal or bluish color, injection of the internal hemorrhoid may be tried although the patient should be told that a permanent cure by this method will probably be unattainable. On the other hand, if the external hemorrhoid is quite large, is irreducible or is fibrotic or grayish in color (Fig. 4), or if the internal hemorrhoid has also prolapsed (Figs. 2 and 9), operation is definitely indicated and, furthermore, is insisted upon.

### PERCENTAGE OF CASES IN WHICH PATIENTS MUST BE OPERATED UPON

Having thus roughly outlined which patients may be handled satisfactorily with injections and those which must be operated upon, it becomes pertinent to know what percentage of each are ordinarily encountered in proctologic practice. Consequently, we have reviewed the classification of 1,056 consecutive patients coming into the Rectal Clinics of the Boston Dispensary and the Cambridge Hospital. The results of this review can be seen by referring to Table 1. It will be noted that 615 or 58 per cent of these patients had hemorrhoids. Of the latter, 161 were double hemorrhoids, the majority of which needed operation. This is 26 per cent of all the hemorrhoids or 15 per cent of the total 1,056 rectal patients. Our percentage of double hemorrhoids is low as compared with other previously reported statistics since all of the cryptic tabs[8] which were formerly diagnosed as double hemorrhoids have been cleaned out of the clinic. There were also some sixteen patients with prolapsed internal hemorrhoids, some of which, may become or even may have already become surgical cases but, as any definite information on this is as yet

TABLE 1*

DIAGNOSIS ON 1,056 CONSECUTIVE ADMISSIONS INTO THE BOSTON DISPENSARY AND THE CAMBRIDGE HOSPITAL RECTAL CLINICS

| By Groups | Cambridge | B.D. | Both Camb. and B.D. | Per Cent |
|---|---|---|---|---|
| Hemorrhoids (primary diagnosis) | 87 | 323 | 410 | .39 |
| Cryptitis, fissures, fistulas, etc | 52 | 220 | 272 | .26 |
| Recto-sigmoidal pathology | 28 | 99 | 127 | .12 |
| Pruritis-ani | 15 | 104 | 119 | .11 |
| Thromboses, misc., exams | 18 | 110 | 128 | .12 |
| Total | 200 | 856 | 1056 | 1.00 |
| Hemorrhoids (secondary diagnosis) | 32 | 173 | 205 | |

CLASSIFICATION OF THE ABOVE HEMORRHOIDS ACCORDING TO TYPE

| | Combined | Per Cent |
|---|---|---|
| Internal (simple) | 438 | .71 |
| Internal (prolapsed) | 16 | .03 |
| Double (simple and prolapsed) | 161 | .26 |
| Total | 615 | 1.00 |

* It will be noted in the upper part of the table that of the 1,056 consecutive cases, 410 had "hemorrhoids" as the primary diagnosis while an additional 205 cases also had hemorrhoids although the latter were secondary to some other more urgent condition. All together, of the 1,056 cases, there were 615 or 58 per cent which had hemorrhoids. In the lower part of the table, these 615 hemorrhoids are classified according to type. It will be observed that some 26 per cent of them were double hemorrhoids in which operation had to be considered. This is 15 per cent of the total 1,056 cases.

unavailable, they have not been included in this consideration.

This review, therefore, shows that approximately 58 per cent of all patients with rectal complaints have hemorrhoids and that at least a quarter of the latter require operation.

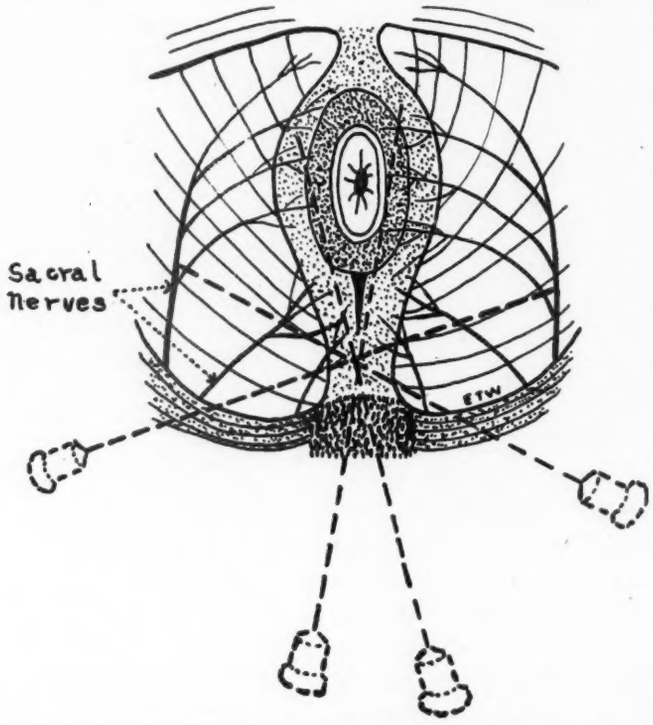


FIG. 5. A diagram illustrating the technic of introducing the oil anesthesia. Through one needle hole in the posterior commissure, the sphincters on each side of the anus, the sacral nerve supplies on each side and the levator-ani in the region of the posterior commissure, can be injected. However, to some it might be easier to inject all of these areas through two needle holes, each to one side of the posterior mid line. This blocking of the sacral nerves with a long lasting anesthetic has encouraging possibilities and calls for further investigation.

## TAKING THE PAIN OUT OF HEMORRHOIDECTOMY

In cases in which a hemorrhoidectomy is necessary, the patient accepts it more readily if he can be assured that it will not require etherization, that postoperative pain has been practically eliminated, that the stay in the hospital is at least one-half what it was twenty years ago and that absence from work will probably not be longer than two weeks. However, there is no miracle in this removal of pain, discomfort and prolonged disability from the hemorrhoidectomy operation. It is a matter of making the operation as simple as possible, of using accepted improvements in technic and of paying attention to details. The following is a list of the more progressive and useful measures in the order of their importance: (1) A posterior sphincterotomy or "pectenotomy"; (2) use of oil anesthesia; (3) all sutures above area of sensation; (4) clean cut, systematic surgery; (5) successful pre- and intraoperative narcosis; (6) regional, spinal and caudal anesthesia; (7) intelligent postoperative dressings; (8) prevention of complications, and (9) management of the postoperative stool.

*Posterior Sphincterotomy.* One of the most important, recent advances in proctology is the posterior sphincterotomy and

our experience has proved it to be a very necessary addition to a hemorrhoidectomy. As the literature covering this operation is not extensive, we will describe it in some detail.

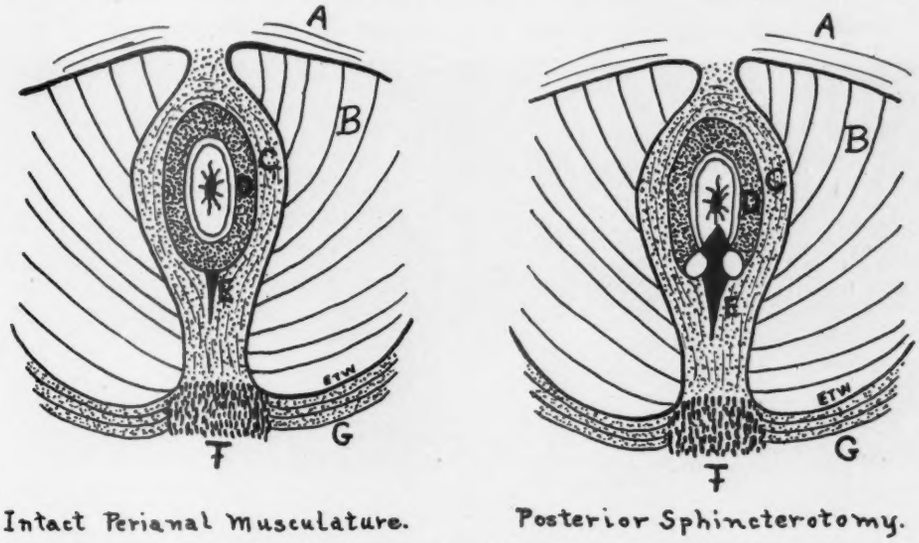


Fig. 6. Diagrams illustrating what is severed as the result of a posterior sphincterotomy. A, the perineal muscles; B, the levator ani; C, the superficial and deep portions of the external sphincter; D, the subcutaneous portion of the external sphincter; E, Minor's triangle or the posterior triangular space; F, the coccyx; G, the glutei. The posterior sphincterotomy simply incises the subcutaneous portion of the external sphincter (D) and also further separates, somewhat, the two legs of the superficial portion of the external sphincter (C) as they go off at a tangent to form Minor's triangle (E) and become attached to the coccyx (F).

The most superficial portion of the external sphincter, called the subcutaneous sphincter ani, is that portion which is felt first by the finger upon entering the anus. It is this muscle which goes into spasm following infection or trauma in this region. Previously, this spasm was overcome by so dilating or stretching the muscle that it became paralyzed temporarily but today such a result is more effectively and safely obtained by means of incising it either at the posterior commissure (Figs. 6, 7 and 8) or in one of the anterolateral quadrants. We prefer the former location.

The left index finger is introduced into the anus up to the level of the intersphincteric septum which is that depression existing between the internal and the external sphincters but detected best in the region of the posterior commissure. The scalpel then incises, by successive strokes, the skin and this subcutaneous portion of the external sphincter at the latter location, each stroke being guided by the left index finger. (Fig. 7.) The internal sphincter and the major portion of the external sphincter are in no way affected as the incision is carried down only to the distal tip of the internal sphincter and passes backward between the two tangential legs of the superficial portion of the external sphincter. (Fig. 6.) Following incision of the muscle, the overlying skin edges are cut back somewhat on each side in order to prevent too rapid reapposition. The severed muscle unites again within a week or ten days and re-epithelialization takes place in from two to six weeks depending upon the amount of skin removed, the depth of the incision and healing powers of the patient. Sometimes cevitamic acid is needed.

We cannot emphasize too strongly the advantages of such a posterior sphincterotomy in a hemorrhoidectomy. It may be done as a first step whenever exposure is difficult to obtain, as obtains in some cases in which the anus is abnormally long and the internal hemorrhoids are far up inside.

But it should always be done either prior to or after the hemorrhoidectomy for the following reasons: It prevents the onset of any postoperative spasm as mentioned above; it prevents edema from forming in the strips of anal skin left between the excised hemorrhoids (Fig. 10); it opens up the anus so that a pressure dressing can be applied and maintained where needed most, thereby eliminating the necessity for intra-anal drains, packs, "whistle tubes," etc.; and finally it quite definitely prevents stricture formation in two ways: first, by so laying the anus open that no false apposition occurs across from one raw area to another prior to epithelialization, and second, it severs any pre-existing fibrous pecten band[9,10] and prevents the premature formation of such a band following the hemorrhoidectomy.

*Oil Anesthesia.* Another important recent advance in proctology is the use of a local anesthetic in oil. When this was first introduced by Gabriel[11] it was greeted with much approval but soon fell into disfavor following the occurrence of sloughs and abscesses. However, the current solutions now in use and their proper employment have been so perfected that the latter are rarities. Personally, we have used between 400 and 500 ampules of a certain oil anesthetic* with only one complication, an abscess out in the buttock which more probably was caused by infection carried there by the needle. We are certain that

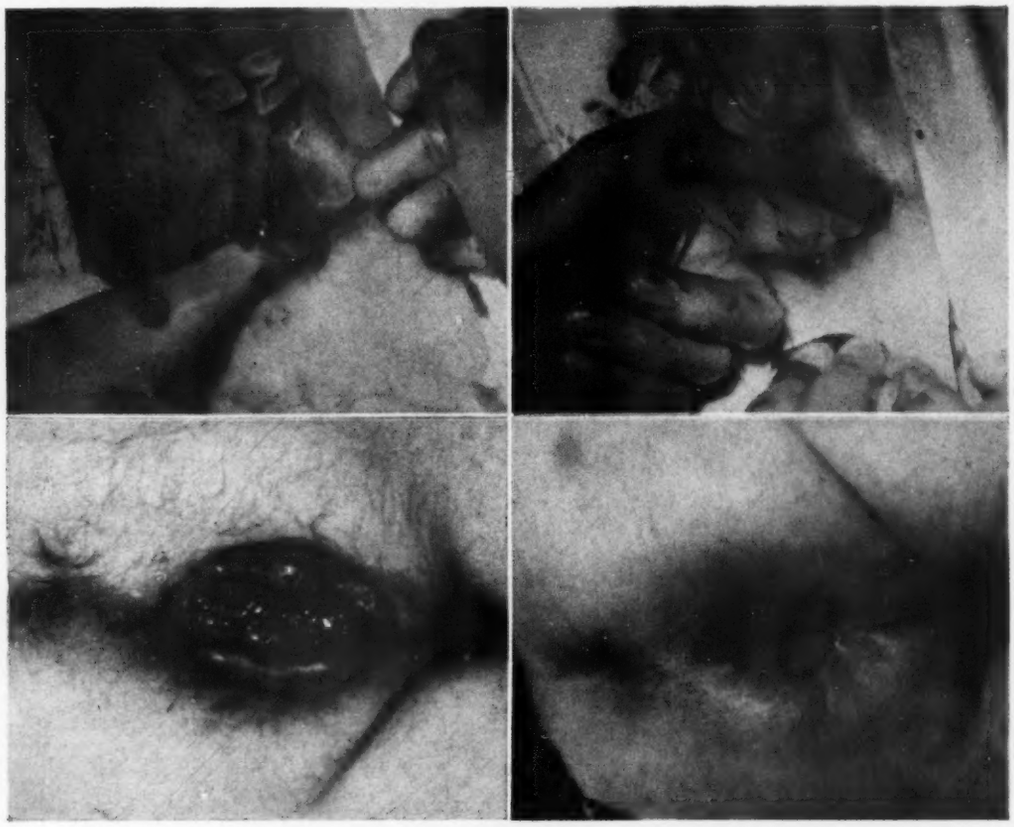

FIG. 7. FIG. 8.

FIG. 9. FIG. 10.

FIG. 7. Doing a posterior sphincterotomy.
FIG. 8. Finish of the posterior sphincterotomy.
FIG. 9. Before operation.
FIG. 10. Three weeks after operation.

* Proctocaine. Columbus Pharmacal Company.

the use of such an anesthetic not only enhances the regional and block anesthesia and the sphincter relaxation during the operation but it also definitely reduces postoperative pain, discomfort, tension and difficulty with bowel movements for at least five days. But to obtain these benefits and to avoid complications, the proper technic of injection is required. The syringe used should be a dry one, the needle a No. 19 gauge, and the site of injection should be resterilized. Only one or two needle holes are necessary about an inch behind the anus. One cc. of oil is injected, from this location into each of five different places: into the sphincters on both sides of the anus, into the sphincters and levator ani behind the anus and out into both buttocks as described later in the description for injecting novocaine. (Fig. 5.) No oil is placed superficially beneath the skin. After withdrawal of the needle, the whole area is massaged well to prevent unavoidable pooling. In many patients an onset of symptoms occurs five or six days postoperatively which is an indication that the oil anesthesia had been operating previously. These patients should be given codeine for a day or two.

*Place Sutures in Non-sensitive Area.* A suture producing tension within the area of sensation at the anus is a constant source of pain for several days, especially upon motion of the gluteal and back muscles. Therefore, the dissection of the external hemorrhoid should be carried up to and beyond the mucocutaneous (pectinate) line so that the suture transfixing the pedicle will be above any area of sensation. Active bleeders should be transfixed, of course, but such transfixations do not seem to have the same disabling effect as do pedicles clamped and tied too low. In the usual hemorrhoidectomy technic, the closure of the anus brings the skin edges together as much as is desired so that any stay or approximating sutures are unnecessary. If the Bacon method[17] is used, it will be seen that the approximating sutures place no tension on the skin edges.

*Clean-cut Surgery.* By clean cut surgery, we mean the careful excision of all so-called cowls, skin tabs, tits of skin, etc., on the edges of the incision as they have a tendency to become edematous and later persist in the form of skin tabs. This applies to any and all methods of performing a hemorrhoidectomy. We herewith present no preference for any one technic other than that it be simple, allow plenty of drainage and produce no tension on the anal skin.

*Preoperative Narcosis.* The secret of a successful preoperative narcosis is the use of small doses of several synergistic drugs at the proper time. There are many variations but the following is an example which has most patients nearly asleep on arrival at the operating room and in slumber by the time the local anesthesia has been injected:

Dilaudid gr. $\frac{1}{32}$ or morphine gr. $\frac{1}{6}$ and
Scopolomine gr. $\frac{1}{150}$–$\frac{1}{200}$ s.c. 1 hour before operation
Seconal or nembutal gr. $1\frac{1}{2}$ p.o. $\frac{1}{2}$ hour before operation

We like dilaudid because it seems to cause less postoperative nausea than does morphine. The proper timing is important as has been made plain by Leigh.[12] The opiates seem to require at least an hour to produce their analgesic effects while the short acting barbiturates require only one-half an hour. In our experience, one-half the dosage of all these drugs should be given to those over sixty, to the frail and debilitated and to those having had cardiac decompensation.

*Anesthesia.* One of the authors (G. A.) prefers spinal anesthesia. This can be given in a small dose to produce only a "saddle" area of anesthesia. It gives excellent relaxation and exposure. Hirschman[13] recommends a caudal anesthesia but we have found the waiting period, before the novocaine "takes," to be irritating. However, the same results can be had with regional and block anesthesia if the proper technic is used. (E. T. W.) From 30 to 50 cc. of 2 per cent novocaine with adrenalin is

required. We have had no one "feel" the adrenalin and its inclusion is very necessary to prevent any allergic or toxic reaction from too rapid absorption of the novocaine. We wish to repeat this admonition: Never inject novocaine, without adrenalin in it, into the tissues about the anus as the blood supply is so great that it can be taken up too quickly. The injection must be made systematically—*under* the peri-anal skin, *into* the sphincters and out *into* the buttocks. A three-inch needle (No. 20 gauge) is quickly inserted through the skin about an inch behind the anus in the posterior commissure and from this one position 10 to 20 cc. of novocaine are injected *beneath* the peri-anal skin nearly all the way around the anus. A little may have to be injected anteriorly through other needle holes. Injecting *beneath* the skin does not abolish the landmarks. Secondly, 5 to 10 cc. are injected into the sphincters lateral to the anus first on one side of the anus and then on the other side (Fig. 5) and also deeply into the sphincters and the levator ani behind the anus. Finally, 5 to 10 cc. are fanned out into each buttock to anesthetize the sacral nerves which emerge from beneath the gluteal muscles, thereby producing a block anesthesia. (Fig. 5.) The left index finger in the rectum guides the introduction of the needle into these various locations.

*Postoperative Dressings.* The postoperative dressings are necessary only to prevent oozing as all major bleeding points are supposedly tied off as mentioned in a preceding paragraph. The posterior sphincterotomy allows pressure by means of dressings to be applied right up to the internal sphincter and in many cases even up to the location of the ligated pedicles. This pressure is held in place by adhesive, not by a T binder. No rubber drains of any kind are needed.

*Prevention of Complications.* The complications of a hemorrhoidectomy include postoperative bleeding, urinary retention, infection and stricture. Postoperative bleeding can be controlled by adequate care of bleeding points and transfixations during operation and by giving an ampule of vitamin K routinely prior to operation in order to overcome any decrease of thrombin production caused by the administration of the barbiturates.[14]

The problem of postoperative catheterization is a serious one in rectal work. The nervous inter-relationship between the anus and the urinary bladder causes pain and spasm of the anus to throw the urinary sphincter into spasm and paralyzes the detrusor muscle. Theoretically, the better the sacral nerves in the buttock are anesthetized by oil anesthesia, the less the urinary nervous system will be disturbed and, of course, all of our pain and spasm preventing measures help. Nevertheless, retention still occurs. However, we have had considerable success in reducing this by using an ampule of doryl[15] prior to catheterization. Woodruff et al.[16] have suggested instilling an ounce of 0.5 per cent aqueous mercurochrome into the bladder at the time of operation to stimulate the detrusor muscle. We have used this routinely in all of our recent cases done under spinal anesthesia with a definite decrease in the need of catheterization. However, in our cases in which local anesthesia is used, mercurochrome is not instilled at the time of operation because catheterization at that time is as bad as it is eight hours later. However, when the latter is necessary we promptly start a urinary antiseptic.

As the result of leaving the wounds open and as the result of the early institution of the hot sitz bath (second day after operation) we see practically no infection. Stricture is prevented in three ways: (1) by care during the operation to leave two or three parallel strips of skin and mucous membrane running up from the peri-anum into the rectum; (2) by the use of the posterior sphincterotomy and, (3) by frequent postoperative digital examinations and the breaking down of false appositions.

*Postoperative Stool.* The postoperative stool is had forty-eight hours after operation by means of an oil retention enema followed in an hour by a saline enema (followed by a hot sitz bath). Mineral oil (½ ounce nightly) is started even before operation and continued until healing is had. This much oil will not leak and does soften the stool.

## MEASURING PROGRESS

Progress in the management of the hemorrhoidectomy can be gauged by examination of Table II which shows how the length of stay in the Cambridge Hospital of ordinary service hemorrhoidectomies has decreased during the past twenty years from 10.7 days in the early 1920's to 7.7 days in the early 1940's. However, when the preventive measures, which we have outlined, are consistently applied, as has been done in our service cases during 1941 to 1942, the length of the hospital stay has been reduced to 4.4 days which is nearly one-half that of the cases at the Cambridge Hospital.

TABLE II*

DAYS OF HOSPITALIZATION OF NINETY-SIX CAMBRIDGE HOSPITAL SERVICE HEMORRHOIDECTOMIES DURING THE YEARS 1921–1942 AS COMPARED WITH FOURTY-FIVE SERVICE CASES HANDLED AS OUTLINED IN THE TEXT

| Cambridge Hospital Service | | | Our Service |
|---|---|---|---|
| 1921–1925, | 1926–1935, | 1936–1942, | 1941–1942, |
| 30 cases | 36 cases | 30 cases | 45 cases |
| 10.7 | 8.3 | 7.7 | 4.4 |

* If we may cite the above figures as a criterion, the ordinary hospital service hemorrhoidectomy was requiring, roughly, an average of eleven days' hospitalization some twenty years ago and less than eight days now. As a result of the various measures outlined in the text, our service cases are confined an average of less than five days.

## SUMMARY

Much progress has been made in the treatment of hemorrhoids during the past few years and, yet, there is still a surprising amount of confusion with reference to the subject among the medical profession.

A review is made of the anatomy, physiology and pathological conditions of the anus and their effect on the genesis of the various types of hemorrhoids.

Selection of the proper form of therapy is discussed. Simple, internal hemorrhoids are injected; frank double hemorrhoids are excised.

A review of 1,056 consecutive rectal cases admitted to the Boston Dispensary and the Cambridge Hospital was made in order to ascertain the percentage having double hemorrhoids and therefore needing operation. Of the 1,056 patients, 615 or 58 per cent had hemorrhoids in one form or another. Of the 615 hemorrhoids, 161 were of the double variety. This is 26 per cent of the total number of hemorrhoids or 15 per cent of the total number of 1,056 patients with rectal complaints. It is concluded, therefore, that approximately 58 per cent of all patients with rectal complaints have hemorrhoids and that at least a quarter of the latter require operation.

When a hemorrhoidectomy is indicated, the layman accepts it more readily when he can be assured that the dreaded postoperative pain, discomfort and disability of the past has been practically eliminated. The latter has been accomplished, not as the result of some new operation, but mainly as the result of using those advances made recently in proctology which are applicable to a hemorrhoidectomy. These are to be found both in the field of technic and in our newer knowledge of the anatomy of the anus. They include the posterior sphincterotomy, the use of an oil anesthesia, careful surgery with the main transfixing sutures above the area of sensation, prevention of postoperative complications and intelligent management of the first stool.

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*Correction:* In the article, "Carcinoma of the Tip of the Tongue," by Dr. Fink and Dr. Garb, which appeared in our October 1943 issue, the authors wish to draw the readers' attention to an error they made on page 141. The sentence, "Ochsner and DeBakey reported a series of 3,047 collected cases of primary carcinoma of the tongue . . . " should have read, "3,047 collected cases of primary carcinoma of the *lung*."

# PREOPERATIVE AND POSTOPERATIVE TREATMENT OF THE TOXIC THYROID*

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THE preoperative and postoperative treatment of the toxic thyroid patient which includes hyperthyroidism, both primary and secondary, Grave's disease, exophthalmic goiter, toxic diffuse goiter and toxic nodular goiter, is a fascinating subject. Its historical development dates back many centuries probably as early as 1000 A.D. In 1170, Roger, at the University of Salnero, Italy, prescribed ashes of sponge and seaweed for goiter, however, the first operation was performed about the year 1000. Writing in 1271, Marco Polo said of the inhabitants of one of the countries he visited: "They are in general afflicted with tumors in the throat occasioned by the nature of the water which they drink." All through the centuries, until the present time, the treatment has varied considerably, and the story of its development is of great interest. The contributions of Kocher, C. H. Mayo, Plummer, Crile and Marine, who were pioneers in the study of the thyroid, are responsible for our present knowledge of the subject. A short résume of the history will not only be entertaining and enlightening concerning the development and treatment of the condition but also reveal that much may yet be learned about this important subject.

## HISTORY

According to Hegner,[1] the early treatment of goiter filled many pages, from transfixing with shoe laces and permitting the ligated masses to slough—this being practiced by Roger Trugardi in 1170—to the cure by the King's touch which was practiced from 1100 to 1600. Andre Dulaurens claimed that his King, Heindriche IV, cured about 1,500 persons annually. A western Arabian of Cordova, Spain, by the name of Albucasis, is credited to be the first to operate for goiter. This was done as stated about the year 1000. Various attempts were made at thyroid surgery throughout the intervening years and Hedenus of Dresden, in 1821, recorded six successful operations for extensive thyroid disease. His record was not excelled for almost seventy years. Kocher studied the gland from an anatomical standpoint and did much for thyroid surgery. In 1874, he did his first total extirpation on a girl eleven years of age. A few weeks later she developed marked changes in character, became dull, sluggish and sullen. After Reverdin reported, in 1882, on two cases of myxoedema ex-extirpatione gland thyroideae, Kocher examined 101 of his cases and took a decided stand against extirpation and it was many years before he performed a bilateral resection.

The description of hyperthyroidism or exophthalmic goiter by Parry (1787), Grave (1835), and Basedow (1840), and of hypothyroidism or myxoedema by Curley (1850), Gull (1875), and Ord (1877) emphasized the mysterious importance of the thyroid gland. Moritz Schiff, a Geneva physiologist, in 1856–1884, made his experiments on the effects of the excision of thyroid in dogs, the prevention of these effects by thyroid grafts and by injection or ingestion of thyroid juices. Because of these experiments he is considered a pioneer of the doctrine of internal secretion and a prophet of thyroid therapy. Coindet, in 1820, was the first to show that iodine was of value in thyroid disorders and in 1850,

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Chatin presented evidence that iodine would prevent endemic goiter. In 1868, Trausseau gave tincture of iodine instead of tincture of digitalis to a patient with exophthalmic goiter by mistake. All toxic symptoms promptly subsided but he thought this was an exception rather than the rule and cautioned against its use in Graves' disease. Eugene Gley, of Evipal, professor of physiology in the Paris faculty, in 1889, demonstrated the existence of iodine in the thyroid gland and the blood. Kocher, in 1904 and 1911, noticed untoward effects in the use of iodine and advised against its use and, because of his wide influence, the drug fell into disrepute. Plummer is given the credit in America for calling attention to iodine in the treatment of exophthalmic goiter.

## PHYSIOLOGY AND CHEMISTRY

To understand the physiology and chemistry is almost essential to treat the condition scientifically. Marine[2] has done much to clarify this, but there still remains many gaps which require further research. Possibly in ten more years a part of the present information will be discarded as obsolete. The greatest advances in the last decade have been in the chemistry of thyroxin and the interrelationship of the thyroid with other organs of internal and external secretion. Ancestrally speaking, the thyroid belongs to the alimentary tract. Its functional activity may be increased or decreased with tremendous capacities as indicated by changes in weight, microscopic appearances, iodine content and blood supply. It has been demonstrated that hyperplasia of the gland indicates hyperactivity but not necessarily hyperfunction. Its chief roll in metabolic physiology is to increase the oxidative processes in the body. The normal human gland weighs from 20 to 25 Gm. and its maximum iodine store is from 20 to 25 mg. (the average normal being 10 to 15 mg.). An interesting factor is that there is a seasonal variation in the iodine storage which is lower in early spring and higher in the late summer. The fetal thyroid readily stores iodine given to pregnant mothers. It is the only organ capable of elaborating the iodine containing hormone; however, iodine is present in the anterior pituitary and in the ovary in significant amounts, but owing to the close relationship now known to exist between these three glands its presence could be of thyroidal origin.

Thyroxin ($C_{15}H_{11}O_4NI_4$) or tetraiodothyronine, was extracted by Kendall in 1916. The mother substance of thyroxin is l-tyrosine. Thyroxin appears to be only the active chemical group of the true hormone which is probably iodothyroglobulin. According to Oswald, there are slight but definite pharmacological differences between thyroxin and iodothyroglobulin. Harrington has estimated that, on an average, 40 per cent of known thyroiodine is in the form of thyroxin and 60 per cent as di-iodotyrosine. Di-iodotyrosine is a stage in the synthesis of thyroxin in the thyroid. This synthesis of thyroxin requires hours while the storage of iodine is almost instantaneous. The form in which iodine is stored is not known. The most characteristic physiological effects of iodothyroglobulin or its active chemical group thyroxin is, that it increases, after a latent period of two hours or more, the oxidation in the body of proteins, fats and carbohydrates and that it also increases the excretion of certain minerals notably calcium and magnesium. The means by which thyroxin increases the metabolism in the cells is unknown. The relation of thyroid to antibody immunity shows no direct association, however, the lowering of iodine store and the tendency to thyroid hypertrophy in many infectious diseases indicates that the thyroid is an important indirect factor in resistance of infections. A diet rich in proteins and fats increases the rate of discharge of thyroxin, and thyroid activity is more necessary in the oxidation of fats and proteins than for carbohydrates. The experiments of Bauman and Hunt demonstrated that thyroid secre-

tion was necessary for the specific dynamic action of foods.

In discussing the relationship of the thyroid to the pituitary gland one notices that the anterior pituitary gland is the master gland and controls the functional state of the thyroid, sex glands, adrenals, and other organs. Since the thyroid enlarges during menstruation, pregnancy and the increased frequency of goiter during puberty, pregnancy and the menopause, it shows that there is a definite thyroid-sex gland relationship. The thymus involutes more rapidly after thyroidectomy, therefore, it must play a factor in the control of this gland. Bodansky believed that the thyroid hormone promotes glycogenolysis and that it is because of this action the hypoglycemic action of insulin is increased after thyroidectomy and decreased by thyroid feeding. This gives its pancreatic relationship. Experimentally, it has been confirmed that prolonged thyroid feeding greatly reduces the glycogen store in the liver. The thyroid hormone also increases the irritability of the sympathetic nervous system, or sensitizes in some way the tissues innervated by it so that they are more susceptible to stimulation by epinephrine. The adrenal cortex and sex glands acting through the anterior pituitary normally exercises some regulatory or inhibitory control over thyroid function. When this control is sufficiently depressed or withdrawn the activity of the thyroid is temporarily increased. Improved water elimination in certain forms of nephritis by the administration of dessicated thyroid, and more recently thyroxin alone or combined with parathyroid extract, shows its kidney relationship. It is used particularly in lipoid nephrosis. There is no explanation except the possibility that these drugs increase the mobilization and excretion of calcium.

The sequence of events as Bard[3] stated them from his recent review of the literature, is that "the fundamental biological significance of the gland seems to lie in its function of aiding the organism in adaptation to changing environment—external and internal such as climacteric alterations, dietary changes and such epochs of special stress a puberty and pregnancy."

## CLASSIFICATION

In order to clarify the subject of goiter, the Committee on Classification of the American Association for the study of Goiter has recommended a clinical classification. This classification has received widespread adoption by the profession and is as follows:

*A. Non-toxic Diffuse Goiter.* This includes the adolescent goiter and colloid goiter. Its treatment consists mainly of prophylactic iodine twice a year and at times thyroid extract or thyroxin alone with the iodine. Surgery is rarely indicated in this type except for cosmetic purposes.

*B. Diffuse Toxic Goiter.* This type of goiter appears ten years earlier than the nodular group. It includes the so-called exophthalmic goiter, Basedow's disease or Graves' disease. Its etiology is unknown. It is not endemic and is associated with the full grown picture of hyperthyroidism. The treatment for this type is surgery.

*C. Nodular Toxic Goiter.* This is the type that usually shows extensive cardiac damage. In many cases they are poor operative risks yet surgery is the method of choice for treatment.

The treatment as set forth in this paper has to do with the diffuse toxic and nodular toxic types which need much study and preparation before surgery can be safely attempted.

## SYMPTOMATOLOGY

The symptomatology of the toxic thyroid may be roughly divided into primary and secondary hyperthyroidism. The primary hyperthyroid cases are those which include the exophthalmic goiter, and occurs usually early in the third decade. The onset is sudden. These patients may show signs of exophthalmos and have a definite stare, however, this is not always a true sign. Hyperirritability, emotional instability, in-

creased heat elimination, nervousness, purposeless movements, tremor of the hands, weight loss with increased appetite, shortness of breath, palpitation and tachycardia are the cardinal symptoms. If a patient early in the third decade of life shows these cardinal symptoms, one can be almost sure that they are dealing with a case of primary hyperthyroidism. The development of eye changes and the tendency for the unrecognized and untreated goiters to develop gastric crises, coma and death differentiate primary hyperthyroidism from the secondary hyperthyroidism due to adenoma.

Secondary hyperthyroidism which includes toxic adenomas has a more insidious onset; 60 per cent of patients are over sixty years of age. There is also evidence of definite cardiac damage with cardiac enlargement, shortness of breath, palpitation and tachycardia. They, too, have an increased heat elimination, weight loss, nervousness, tremor and definite fatigue. Any patient falling into any one of these two groups should be given thorough study because surgery will undoubtedly be the method of choice in treating these unfortunate individuals. Many mistakes have been made in confusing this condition with heart disease, hypertension, neurosis, pulmonary tuberculosis, acute abdominal states and certain apathetic conditions.

The various methods in common use today to determine the extent of toxicity and also the degree of damage done by this toxicity are definite guides in the preoperative treatment. These tests include fourth hour temperature and pulse readings, complete blood count, blood cholesterol, urea nitrogen and sugar determinations, complete urinalysis, electrocardiogram, roentgenography, laryngoscopic examinations, blood pressure, frequent weight readings, basal metabolism rates, compliment fixation tests for syphilis and other less frequently used tests such as the hippuric acid test for liver damage. A correct analysis of the data obtained by these foregoing tests together with the therapeutic use of iodine and daily observations of the patient decide whether or not the patient is one who requires surgery and one who will be a safe operative risk.

To be able to diagnose a condition is probably the most important phase of medicine but often times the literature is much too voluminous in the clinical aspects of the disease and too little is said of treatment, at least proper treatment. This is true of the toxic thyroid.

## PREOPERATIVE TREATMENT

The proper care of the toxic thyroid must begin with the general practitioner who usually first sees the patient. He must be on the alert because many of the patients show very little signs and symptoms. When he has made the diagnosis he must be frank with the patient concerning the proper course to take for future treatment. He should not be an alarmist but must be firm enough to convince the individual that the advice of a specialist must be obtained. No preliminary medication should be given except possibly mild sedatives and advice about proper diet and rest nor should any medication containing iodine be given. The physician's next step should be to select a good surgeon, one who is considerate and one who operates in the most pleasant surroundings. This is discussed thoroughly with the patient and this discussion should be such that the individual will have a feeling of confidence before he has been definitely referred to a clinic for future study. An early appointment should then be made so that the patient does not have time to fret and worry. A personal letter of introduction often helps because the patient will feel that there is something in common between the referring physician and the specialist group.

Conklin[4] claims that to carry out successfully a program which gives the patient psychic support and keeps emotional upsets at a minimum in the preoperative care, it is highly desirable that this preparation be confined to a small group of

experienced men who have charge of all patients with this disease. He believes also that the preoperative preparation of the goiter patient can best be directed by a small group of men with the co-operation of the surgeon in charge of the case. The close co-operation of an experienced internist with the surgeon in the original examination of the patient, in the diagnosis and evaluation of the degree of hyperthyroidism, during the preoperative regimen and in making the decision as to when surgery can most safely be performed is most desirable, in fact, the internist can usually spend more time in the direction of the details of the goiter patient's preparation and thus is better fitted than the surgeon to have major charge of the preoperative management.

Even though a complete history is imperative, the original history may be only cursory and can be completed at subsequent visits so that the patient is not unduly tired or excited by this or a thorough physical examination. The history should include the age at which the patient first noted the goiter, and the elucidation of the symptoms of toxicity and their duration is also important. Weight loss in spite of a good appetite is also important to elicit. One must also determine whether or not iodine has been taken, how much and over how long a period of time this medication was given. If the patient has improved under iodine therapy, it is important evidence of the toxicity of the gland. Reassurance is a prime essential in the goiter patient and at the original examination the patient should be given encouragement, assured as to the ultimate outcome and told just what studies are to be carried out and the reasons for these studies. Conklin[4] also states that this résume of the coming examination will aid greatly in obtaining the maximum co-operation and the minimum psychic upset caused by encounters with unfamiliar procedures. The patient is carefully admitted without delay. As soon as the patient is comfortably situated no more is done that day. The routine orders, such as complete blood count, urinalysis and fixation tests, are ordered for the following morning. If the patient is not too nervous, the breakfast is delayed and a basal metabolic rate determined. This should be spoken of as the "breathing test" and the details of the procedure outlined so that it will not alarm the patient. This may be delayed until the second morning when possibly a more accurate test can be obtained because the first night in the hospital may be a restless one, thereby giving an untrue reading. The metabolic rate should be repeated the following day. The usual house diet is ordered for the first few days. A fasting blood sugar, also a blood urea nitrogen and blood cholesterol determination are made in the first few days. After the basal rates are obtained, such examinations as the routine larynx examination is made by the laryngologist who also makes sure no upper respiratory infection is present. Because of the danger of injuring the recurrent laryngeal nerve causing vocal cord paralysis, it is always advisable to know whether or not the vocal cords are in good condition before operation. If a substernal thyroid is suspected, a roentgenogram is made to determine the extent. It is wise in most cases to have the cardiologist examine the heart muscle and take an electrocardiogram but this is not necessary in every case. Any other laboratory tests that are necessary are made at this time. From this information the patient is put on a fairly strict routine that must be carried out from day to day.

Iodine plays the most important rôle in preoperative therapy. Under no circumstances should it be given unless operation is anticipated or agreed upon because of the false security it may give the patient and deleterious effects it may have upon the gland itself. Marine and Plummer are responsible for establishing order where chaos previously prevailed with regard to the successful cure of hyperthyroidism. In 1912, Marine[6] claimed that the use of

iodine would temporarily cause a reversion of the hyperplastic gland to the colloid state and with it a short respite in the toxic symptoms. During this time surgery could be done with comparative safety.

Remington[7] stated that the normal thyroid gland contains about 10 mg. of iodine at a concentration of 40 mg. per cent by weight. This is found principally in the colloid, according to Van Dyke.[8] The normal iodine content of human blood is about 12 micrograms per cent; this means that the normal blood contains about 120 parts of iodine per billion. Curtis[9] has shown that the blood iodine as a rule is increased in patients with hyperthyroidism, however, about 10 per cent of the determinations may fall within the higher normal range. The average increase to 27 micrograms per cent is greater in patients with diffuse hyperplastic goiters, with or without exophthalmos, than with toxic nodular goiters, the average in the latter being 22 micrograms per cent. The increase is accentuated by menstruation and pregnancy.

Kolnitz and Remington[10] have shown that there is a correlation between the season of the year and the weight and total iodine content of the thyroid. The summer glands are both heavier and richer in iodine but the percentage of iodine remains practically constant.

After iodinization with Lugol's solution or any form of iodine thus far investigated there ensues a sharp increase in the hyperiodenia (Curtis).[9] This increase is principally in the organic fraction and is due to the medication, while there is a decrease in the alcoholic insoluble organic fraction. Thus the circulating thyroid hormone is presumably lessened. Iodine and thyroid function are inseparably related since the thyroid is the principal storehouse of iodine.

Curtis and Puppel[11] have shown that the utilization of iodine to form thyroid hormone is thus an integral part of the thyroid activity. As a consequence the metabolism of iodine becomes of fundamental significance in the investigation of thyroid physiology and of the changes in function incident to the development of thyroid disease. The above authors also bring out four features of metabolism of iodine in exophthalmic goiter: first, the thyroid gland iodine is decreased in untreated cases; second, the blood iodine is usually increased in untreated cases; third, the urinary secretion of iodine is usually increased; and fourth, exophthalmic goiter presents an increased negative iodine balance. Patients with toxic nodular goiter present an even greater negative iodine balance due to a greater urinary excretion. Nevertheless, the excretion of iodine in the feces and sweat is greater in exophthalmic goiter.

Immediately following thyroidectomy, a rise in the blood iodine of non-iodinized patients occurs. There is usually a fall in the level following thyroidectomy on patients treated with Lugol's solution or some iodine preparation. The blood iodine then remains irregularly increased as long as postoperative iodine is continued. Subsequent to an adequate thyroidectomy for hyperthyroidism and the cessation of postoperative iodine, the blood iodine eventually decreases to a low normal level. This blood iodine relationship of exophthalmic goiter is similar to that of toxic nodular goiter. Two evidences then of iodine deficiency are thus demonstrated in patients with hyperthyroidism, first, the decreased iodine content of the thyroid gland, and, second, the increased loss of iodine in the urine. Further evidence of the deficiency is shown by the usual response to iodinization which is really a form of replacement therapy. Means and Lerman[12] stated that the clinical facts regarding iodine in thyrotoxicosis is that, it produced an altogether characteristic and specific response which consists of an amelioration of symptoms and a drop in metabolic rate. This response will occur at any state of the disease. It also appeared that the response had no relation to the duration or direction of progress of the disease but

merely acted as a check on the intensity of its symptoms.

These clinical facts are consistent with the theory that in the toxic thyroid, the thyroid allows the escape of thyroxin to precede at an excessive rate and the cells of the gland hyperfunction in consequence. It is suggested then that iodine sets up a temporary barrier to this excessive outflow and checks the leakage of thyroxin from the gland. The known facts of iodine and thyroxin content of the blood, urine and gland bear out this theory. Means and Lerman[12] also believe that refractiveness to iodine is apparent and not real and that, if the truth be known, those patients in whom iodine has no effect are already iodinized. Curtis[9] also stated that by investigating this iodine metabolism it is becoming possible to leave the earlier empiricism and to adopt a more scientific technic of the use of iodine in both the treatment and prevention of thyrotoxicosis.

The form in which iodine is used is of no particular importance because it is active in any form provided the minimum effective dose or more is given. Plummer[13] introduced iodine in the form of Lugol's solution in 1922 and this is probably the most commonly used preparation today. The average dose is minims 5 to 20 (.3 cc. to 1.2 cc.) three times a day and Guthrie and Conklin[14] use from 10 to 15 minims (.6 cc. to 1 cc.) according to the toxicity of the case at hand. The response to ethyl iodide and potassium iodide is essentially the same as that of Lugol's solution. The potassium iodide is given in a saturated solution, 10 minims (.6 cc.) three times daily. Iodine may be given by mouth, rectum or vein and is equally effective in all three routes. Jones[15] recommended intravenous iodine in the form of sodium iodide because it can be pushed faster in cases of thyroid storm and in those cases showing gastrointestinal symptoms which would be aggravated with the drug by mouth.

Wetherell and Groat[16] advised that when iodine is administered over long periods of time, its administration should be interrupted for a week or ten days every four to six weeks.

When iodine is intensively administered to a patient with hyperthyroidism, previously untreated with iodine, a marked clinical remission in the course of the disease is noted in seven to ten days and usually continues for two or three weeks. It is during this clinical remission that operation should be performed, because it has been definitely demonstrated that the mortality rate has been reduced to practically nil if surgery is done at this time. Poste[17] claimed that there are three things to watch for when giving iodine: first the slowing of the pulse rate; second, the amelioration of symptoms; and third, the hardening of the thyroid. If these three things occurred there will undoubtedly be a drop in the basal metabolic rate and the operation will be safe.

Goetsch[18] stated that if operation is not done during this remission, the patient often relapses into a state of clinical exacerbation in the course of one, two or three months and a condition of uncontrollable hyperthyroidism may result. Spontaneous hyperthyroid crisis which occurs occasionally in the course of the disease may be controlled by large doses of iodine, but when a crisis occurs as a result of the incorrect use of iodine, the further administration of iodine, even in greater amounts, is ineffectual and the patient may die.

Many individuals take iodine without the advice of the physician and because of this Guthrie[19] stated: "The public should be warned of the great danger in the self administration of iodine for the treatment of goiter, and physicians should have a clear understanding of the types of goiter that are amenable to the iodine treatment and of the danger which attends its incorrect use."

A false impression may be obtained in stating the number of days required to prepare a patient properly, however, in a series of 100 cases selected from the files

of the Guthrie Clinic during the years 1938 and 1939, eleven days was the average. A few patients were ready in less time and a large number required as long as two to three weeks. This clinic has spent as long as seven or eight weeks to make the patient safe for operation, therefore, no definite time limit should be set. The subject of rest should be thoroughly outlined for the aged, those with severe toxicity and those showing cardiac decompensation. The patient is awakened about 7 A.M. and breakfast is served. The patient should then stay in bed until about 10 A.M., when he is allowed out of bed for about one hour. This gives plenty of time to rest awhile before having dinner. The afternoon is broken up by allowing activity for two hours sometime in the mid-afternoon. The patient is again put to bed for rest before the evening meal and made to stay for the balance of the evening until time to retire. This should not be later than 9 P.M. A large number of patients, who do not show cardiac decompensation, and are younger and have a mild or moderate degree of toxicity, are allowed to be up and about as they desire. This added freedom seems to benefit them more than the bed rest routine. If sleep is difficult, a mild sedative, such as, sodium bromide gr. 15 (1 gm.), phenobarbital gr. 1½ (.13 gm.), seconal gr. 1½ (.13 gm.), amytal gr. 1½ (.13 gm.), or nembutal gr. 1½ (.13 gm.) may be used. In more severe cases morphine sulfate gr. ⅙ (.011 gm.) may have to be given at bed time, however, this should not be carried out over a long period of time because of the danger of addiction. If the patient shows extreme restlessness during the day, a mild sedative, such as elixir of phenobarbital drachms 1, (4 cc.) three or four times during the day, may be helpful. If the patient does not tolerate the phenobarbital, 10 gr. (.66 gm.) doses of sodium bromide may be given instead. When various tests are to be performed, such as basal metabolism rates and tests on the fasting blood they should be explained to the patient so that he will not be made unduly nervous by them.

Rest is probably one of the most important parts of the treatment especially in those patients showing cardiac damage because it helps to build up a definite cardiac reserve. Noland and Payne[5] claim that this cardiac reserve should really be the first concern in preoperative preparation. They recommended sodium bromide or one of the barbituates, however, they warned that the barbituates, in elderly patients and those with psychological tendencies and in the emotionally unstable, may produce a maniacal outburst. If this is suspected, morphine should be given and should also be given to those patients who are on the verge of crisis or delirium.

The diet should be of high caloric content, mainly carbohydrates. These carbohydrates help to safeguard the liver through glycogen storage. Means, Hertz, and Lerman[20] claim that excess protein in the diet is undesirable because of its specific dynamic action—it raises the metabolism. There is no specific indication for fat and may be given to whatever extent the patient demands. Soskin and Musky[21] reported the case of a patient treated on a high fat diet because the patient refused operation. This diet consisted of 2,790 calories made up of 230 Gm. of fat, 90 Gm. of protein and 90 Gm. of carbohydrates. This patient showed marked improvement. This is the report of only one case and is not generally recommended. Vitamin B in the form of yeast or some other preparation may be given routinely. It is of value in improving the general nutrition because it helps to increase the appetite. The diet used at the Guthrie Clinic is a balanced one containing sufficient carbohydrates to insure an adequate glycogen reserve and at times is strengthened by advising the patient to eat plain rock candy.

Patients with diabetes mellitus have definitely been made worse by their toxic thyroid, and insulin must be used to a greater degree than in a case of uncom-

plicated diabetes. The amount of insulin, of course, should be determined by frequent fasting blood sugars and frequent urinalysis. Rudy, Blumgard, and Berlin[22] recognized the fact that diabetes mellitus was aggravated by thyrotoxicosis and benefited by myxedema. These men also stated that a severe case of diabetes mellitus which was not controlled adequately by application of usual therapeutic measures was somewhat relieved by a total thyroidectomy, however, they do not advise this routinely for diabetes mellitus.

The daily fluid intake should be at least 3,000 to 3,500 cc. This may be taken by mouth if well tolerated. In toxic cases 5 per cent glucose in normal saline given at the rate of 60 drops a minute is of great value in rebuilding the depleting glycogen reserve of the liver and replacing the rapid loss of fluid by skin and respiration. This glucose should not be given continuously in normal saline because of the danger of producing edema. Frequent blood chloride determinations should be of help in this respect. Another cause of edema which may be confused with too much chloride intake is protein deficiency. This may be determined by the serum globulin albumen ratio. If it is a protein deficiency, small frequent blood or plasma transfusions should be given. Fluids and glucose should be pushed to a greater extent several days prior to the anticipated day of operation in order doubly to protect the patient against dehydration and liver necrosis which may follow immediately after surgery. As a matter of academic interest only, Thomas and Alexander[23] state that the concentration of protein in the cerebral spinal fluid is within the lower limits of normal in most cases of exophthalmic goiter and usually shows a marked increase with association in gain in weight and reduction in basal metabolism following a subtotal thyroidectomy. This, of course, plays no active part in the preoperative treatment of this condition.

After the first World War some believed that diathermy and ultraviolet rays could alleviate the symptoms of hyperthyroidism in the same way as roentgen therapy, however, Jackson,[24] in 1930, definitely stated that physical therapy has a definite place in medicine but not in the treatment of goiter.

The laboratory plays an important part in the diagnosis and treatment of most diseases and toxic goiter is no exception. The information thus obtained acts as a safe guide to treatment. Plummer[25] did extensive blood studies in 1918, such as hemoglobin, red and white blood cell counts and complete differentials, but found only one significant fact and that was a mononucleosis. Mahon[26] studied patients prior to operation, at the highest level of their postoperative reaction and again in three weeks but could draw no definite conclusions. He did bring out the fact that the sedimentation speed indicated the degreee of toxicity and that it was particularly helpful to control therapeutic effects or a treatment, especially roentgen irradiation. This test is used very little routinely.

Another popular test is the blood cholesterol determination. It is low in toxic thyroid states and is brought to a normal level partly by preoperative treatment but chiefly by subtotal thyroidectomy. Hurxthal[27] stated that the blood cholesterol determination is of distinct but limited value in the diagnosis of hyperthyroidism. The lowest values are found in those patients in or near a thyroid crisis. Hurxthal[28] also stated that the value in all types of exophthalmic goiter is lower than in toxic adenomatous goiter. Recurrent hyperthyroidism is associated with cholesterol values that are almost as low as those in exophthalmic goiter. McElroy, Schuman, and Ritchey[29] made the statement that while there is a general tendency for the cholesterol values to be low in hyperthyroidism, they could not demonstrate any definite inverse relationship between the degree of toxicity as measured by the basal metabolic rate and the serum cholesterol level.

Various other laboratory procedures such as complete urinalysis, fasting blood sugar determinations, blood urea nitrogen, fixation tests and serum-albumen ratio, are used mainly to determine the general condition of an individual and guide only the supplementary treatment of hyperthyroidism in case any of these tests should show abnormalities.

Very little will be said about the basal metabolic rate because most all agree as to its necessity in diagnosis and in the progress of treatment. It is not an absolute criterion as to the patient's general condition but should be correlated with subjective and objective symptoms as well. In the preoperative preparation, it is hoped to decrease the metabolic rate to a figure somewhere near or within the normal limits of plus 15 to minus 15. One reading alone should not be relied upon but the first reading should be followed by a second the following morning. No test will be altered as much as the basal metabolism rate by such things as nervousness, fright, suspense, and fever, therefore, the patient should have a complete explanation of how it is done. It should be referred to as the "breathing test" and the patient told that several will be taken during the course of the preoperative preparation. On the morning of the test, the patient should not be allowed breakfast and should be taken to the metabolism room on a carriage with as little effort as possible expended. It should be repeated every four or five days and if the treatment is adequate and proper, a gradual drop will be noted. The breathing test may also take part in the anoci-association which will be spoken of later. Jackson[30] stated that the metabolic rate is not an index of the risk of operability but it gave diagnostic evidence of the presence or absence of hyperthyroidism. The test may furnish valuable information to the surgeon if it is made by a reliable machine, a reliable technician and under proper conditions. Goldberg[31] suggested that a consideration of the circulation time and blood cholesterol in addition to the conventional metabolic test afforded a more accurate and balanced interpretation of the state of thyroid function than dependence on one method alone. To show further that the basal metabolism rate should be considered secondarily, Andrus and McEachern[32] may be quoted as follows: "The beneficial effect of iodine upon the clinical disease is primarily upon the thyroid gland and only secondarily upon the metabolic phenomena resulting from the excessive thyroid secretion." Therefore, before an attempt is made to interpret the results of metabolic studies the surgical and medical staff should be thoroughly versed in clinical studies of thyroid disease.

The management of the thyroid heart should be mentioned in preoperative treatment. The heart may show anything from a mild tachycardia to decompensation with marked arrhythmia. Ruddock and Toland[33] stated that digitalis should be used only in those cases that show decompensation and not in the compensated ones. Noble and Chen[34] pointed out that digitalis is useless in thyrotoxic tachycardia unless cardiac failure is present. Thevetin injected intramuscularly in the dosage of three to nine cat units has been suggested to subdue the cardiac activity during the preoperative period. The Eggleston method of dosage for complete digitalization is the usual standard method. A rough easy modification as given by Ruddock and Toland[33] is .2 gr. or .01 Gm. of the powdered leaf per pound of body weight. This gives the theoretical total amount for complete digitalization. This should be done only if no digitalis has been given for ten days. If the patient has received digitalis in the preceding ten days, the total calculated dosage should be reduced, the amount of digitalis retained allowing an average of 2.2 gr. excreted each day. If this cannot be done then the total dosage is reduced to 75 per cent and the Eggleston method followed. Quinidine sulfate is best given on the third or fourth postoperative day and will be mentioned later. Anderson[35] made no attempt to use

it preoperatively. From the cardiac standpoint, the time to operate is when all signs of decompensation have disappeared which is usually seven to ten days after complete digitalization. To wait longer may again subject the individual to those influences that caused the original decompensation, namely, thyroid dysfunction.

Roentgen therapy has no place in preoperative preparation and should not be used where surgery is contemplated. It has its place in treating inoperable cases and certain selected cases, especially where operation is refused. Grier[36] believed that it might be used in intrathoracic goiters with or without hyperthyroidism if operation is considered inadvisable. The irradiation may reduce the size of the gland and relieve pressure symptoms.

After placing the patient on the foregoing routine and having completed the laboratory studies, when is the patient ready for operation? According to Thompson and associates[37] two main factors influence operative mortality and they are the condition of the patient and the skill of the surgeon. These principles appear very fundamental but require thought. Experience is the answer. No well managed clinic will hurry operation or employ unskilled operators. There are all degrees of hyperthyroidism, from the mild case to the case with impending crisis or where crisis has already occurred. For this reason each patient is an individual problem. Lahey,[38] in 1937, reported on 13,000 cases with 15,200 operations. In this series there were 111 deaths; 40 per cent died of thyroid crisis, 10 per cent of cardiac conditions, 10 per cent of embolism and the remaining died of carcinoma and unrelated conditions. He also believed that when a thyroid crisis eventuated, some other factors have become involved as indicated by the frequent and quite sudden occurrence at this time of a different group of symptoms; namely, vomiting, diarrhea, and temperature elevation 105 to 106°F. These other factors have to do with liver effects because of the low glycogen found in patients dying with hyperthyroidism and by the fact that these individuals are so often dramatically benefited by the constant use of measures combating lowered liver function, intravenous glucose and fluids. Many surgeons do not agree with Lahey who advises operation if there is no improvement after three or four weeks' preparation. Most men agree that where the symptoms are becoming more intense, immediate operation is necessary. Lahey[38] further stated that any patient with cardiac damage shown by mild failure or cardiac arrhythmia should be operated upon immediately without preliminary preparation by non-operative measures, and that in almost all cases one can promise relief from incipient heart failure, a striking increase in cardiac capacity as related to suspended activity. By giving quinidine for a few days after the patient has been freed of the hyperthyroidism by operation, there is a restoration to normal cardiac rhythm in over 70 per cent of the cases. All men do not agree with this train of thought.

In cases of pregnancy and diabetes it is wise to consider immediate operative intervention because of the danger of crisis as these conditions are allowed to advance. If crisis is threatening in severe hyperthyroidism, early surgery may be advisable. The alternative is to evaluate early signs and give 40 to 60 minims of 5 per cent glucose in distilled water intravenously per minute, day and night, together with 50 per cent glucose so that the individual will receive from 500 to 600 Gm. of glucose in twenty-four hours. Where vomiting and delirium have occurred 50 minims (3 cc.) of Lugol's solution in 1,000 cc. of fluid intravenously should be given. Some men believe that to operate on one who has recently suffered and recovered from a crisis is to court disaster but again Lahey[38] disagrees in this diction. He advises a high carbohydrate diet for two or three weeks and stage operations with six weeks between stages. The stage

operation is seldom necessary now since modern therapy has been instituted with the aid of iodine, but still is a very useful procedure.

Lehman and Shearburn[39] stated that no quantitative rule governing the duration of preoperative treatment can be laid down and the individualization is an essential element in the successful handling of toxic thyroid disease.

Thompson and his associates[37] have shown that it is unwise to advise surgery when the patient fails to gain or lose weight, where the emotional instability and muscle weakness are marked, where the basal metabolic rate is plus 60 per cent or higher in spite of the administration of iodine, where the disease is increasing rapidly in severity, where less than two weeks have elapsed after an upper respiratory infection has cleared up, and where cardiac decompensation is present. The foregoing conclusions are contradictory to some already stated which further emphasizes the fact that individualism is the method of choice.

A modified anoci-association technic is of extreme value because the patient, especially the emotionally unstable and irritable ones, will go to the operating room in a much better condition. Crile[40] was the first to use this technic of "stealing the goiter." The method used in the Guthrie Clinic is as follows: The term operation is never used and the word treatment is substituted in its place. Several days before the planned operative day the patient is given either a sterile hypodermic or morphine gr. $\frac{1}{8}$ (.0082 Gm.) in the early morning. It is explained to the patient that this is part of the treatment and can be given only hypodermically. A day or two before operation the patient is taken to the basal metabolic room for a metabolism and this helps further to alleviate the patient's fears because, on admission, two metabolism tests were made on successive days, and perhaps one or two in the preoperative régime. The morning of the operation the breakfast is delayed as for a metabolism test and one or two hours before the operative time sodium amytal, gr. 6, (.396 Gm.) is given. The patient usually goes to sleep and does not waken until after the operation. The preoperative medication of morphine sulfate, gr. $\frac{1}{6}$, (.011 Gm.) and atropine sulfate, gr. $\frac{1}{100}$, (.00066 Gm.) is given thirty minutes before the operation. To make this method further fool-proof the operation is not listed until late the evening before and the nurses are instructed not to deviate from their regular routine care in any way. The family is not allowed to see the patient the morning before surgery but is advised of same several days in advance so that they may be present that morning.

Many anesthetics are used but the ones of choice are either ethylene or cyclopropane. Local anesthesia with novocaine is used widely in some clinics, but according to Guthrie and Woodhouse[41] it has little place in thyroid surgery and that the toxic effects produced by ethylene are minimal and of little consequence in comparison to the deleterious effect of an operative procedure on a conscious patient who is terrified by the manipulations attendant to a thyroidectomy, and whose terror is graphically evidenced by a mounting pulse and a state approaching crisis. Ethylene is used in this clinic and is given by anesthetists well trained in the administration of thyroid anesthesia. It has several advantages, the main ones being the margin of safety, the lack of dehydration which certain other anesthetic agents cause by a leaking skin, the quick response of the patient after the anesthetic has been stopped, the quiet, regular respirations without the secretion of mucus and the absence of anoxemia. It gives sufficient relaxation for goiter surgery because very little more than actual analgesia is required.

The Guthrie Clinic has had over 483 goiter operations without a single death and the main reason is because each patient is considered an individual problem. Guthrie reported, in November, 1940,

on the last 1,383 thyroidectomies in which the mortality rate was only 0.65 per cent. In the last thirteen years there has been only one ligation and only twenty stage operations in the 1,383 cases. This is an incidence of 1.45 per cent for stage operations. Of this group of 1,383 cases, 1,040 were considered toxic and of this number there were only eight deaths or a mortality of 0.77 per cent.

Richter[42] reported 270 consecutive one stage thyroidectomies on thyrotoxic patients over fifty years of age, without a death. In the same period of time, 900 thyroidectomies in every age group were performed with three deaths or a mortality of 0.33 per cent.

In summing up the paper thus far, it may be said that after complete evaluation of the patient's signs and symptoms, a reduction of the basal metabolic rate, after the weight loss has been checked or shows a gain, after the nervousness has been lessened and all contributory factors such as cardiac decompensation or associated diseases have been brought under control, the patient is ready for surgery and should be considered a safe risk.

### CERTAIN PRINCIPLES OF OPERATIVE TECHNIC

The actual technic of the operation will not be discussed except to say that a low collar incision is used in this clinic. The operation should not be hurried but should progress as rapidly as is compatible with a well trained surgical team. Subtotal thyroidectomies rather than complete thyroidectomies are the rule in this Clinic because it helps prevent postoperative myxedema and injury to the recurrent laryngeal nerves and the parathyroids. All clamps are placed horizontal to the neck to help safeguard the nerve which is never deliberately exposed, as advised by Lahey.[43] The suture material used by Guthrie is fine silk and more recently cotton. This helps to prevent serum accumulations and drains are rarely needed. Clips are used to close the skin and no attempt is made to suture the fine platysma muscle. The type of dressing used in this Clinic has proved very satisfactory. A dressing moistened in saline solution is placed above and below the clips. A dry dressing is placed over these covering the clips, and an oblong piece of sterile rubber sponge is placed so as to cover the entire incisional area. Sterile cotton wadding is next added and all held in place by a wide gauze bandage which is wrapped firmly about the neck and does not go under the armpits. Two long narrow strips of adhesive are then placed, each starting at the back and coming around the front of the bandage to the chest wall of the opposite side. This dressing is removed in twenty-four hours together with one-half of the clips. The remainder are removed in forty-eight hours. A simple gauze dressing is used after the first twenty-four hours and is removed on the fourth day. Mayo and Simpson[44] suggested the use of a sea sponge. During the operation, atropine gr. $\frac{1}{100}$ (.00066 Gm.) to $\frac{1}{200}$ (.00033 Gm.) is given if the skin shows signs of leakage and coramin or adrenalin are used as heart stimulants, if necessary.

Jackson[45] stated that there are six immediate complications of thyroid surgery: These are injury to the recurrent laryngeal nerve, hemorrhage, injury and collapse of the trachea, air embolism, acute hyperthyroidism and anesthetic complications. The treatment of these conditions is prevention, air embolism being one of the most dreaded complications. Guthrie and Evans[46] reported on a questionnaire sent to thirty-eight experienced thyroid surgeons. The result was, twenty-three had experienced no cases of air embolism and fifteen had twenty-one cases of air embolism. Of the twenty-one cases there were thirteen recoveries and eight deaths. Of these eight deaths, two were in block dissection of the neck and six were in cases of thyroidectomy. The best treatment is prophylaxis but, if it does occur, artificial respiration should be started immediately and continued. Intracardiac injections of adrenalin may be helpful.

### POSTOPERATIVE TREATMENT

The postoperative care which is as equally important as the preoperative care is now begun and the goiter team should not relax their close supervision of the case. The surroundings must be quiet and the family made to understand that for the next few days they should not bother the patient. A semisitting posture in bed with the head made comfortable with small pillows is the best position. Liquids are allowed as soon as tolerated with the exception of stimulants such as tea and coffee. In order to make up the fluid loss a proctoclysis of tap water is started immediately and continued until the patient is taking sufficient fluids (3,000 to 3,500 cc. daily). Thirty minims (1.85 cc.) of Lugol's solution is placed in the first 1,000 cc. of the proctoclysis. Intravenous and subcutaneous fluids are resorted to only if absolutely necessary because of the discomfort they cause. In the first two days morphine sulfate gr. $\frac{1}{6}$ (.011 Gm.) and atropine sulfate gr. $\frac{1}{100}$ (.00066 Gm.) are given every four to six hours to combat restlessness and pain. A number of these patients do not realize that they have been operated upon until many hours after they have been returned to their room.

Many patients have considerable mucus in the respiratory tract which makes breathing difficult and uncomfortable. Means[47] suggested the use of compound tincture of benzoin or steam inhalations. A tube is placed in the mouth so that the patient may directly inhale the fumes. Hyperventilation with 95 per cent oxygen and 5 per cent carbon dioxide is also used to help patients raise this mucus. It is employed in the Guthrie Clinic routinely where indicated and may be done several times a day until the mucus definitely decreases in amount. Haines and Boothby[48] suggested oxygen therapy, in 1929, for patients having severe reactions after thyroidectomy, especially those with cyanosis resulting from pulmonary edema, bronchopneumonia and laryngeal or tracheal obstruction. In their series of cases there was marked subjective improvement, usually the fever subsided rapidly and the pulse and respiration rates were decreased. Dyspnea was partially or completely relieved.

The oxygen tent is used extensively in this clinic and often times the patient is placed in one immediately after operation if there are any signs of respiratory or circulatory embarrassment and it is used almost entirely in the severe hyperthyroid cases to prevent postoperative reactions. An exaggerated postoperative reaction calls for large doses of sedatives, glucose, cold applications and the oxygen tent. The free use of ice bags to help reduce the hyperpyrexia is also valuable. It has been suggested that one ice bag should be used for each degree of fever.

Postoperative tachycardia need not cause alarm if the pulse is regular and hyperpyrexia and restlessness are absent. Some of the older patients will develop cardiac irregularities three or four days postoperatively and if this does occur quinidine sulfate is given. A test dose is first administered and if there are no ill effects 5 gr. (.33 Gm.) are given every four hours, day and night, for twenty-four hours. The pulse is counted before each dose and, if regular, the drug is stopped. If no improvement is noted after twenty-four hours, 5 gr. (.33 Gm.) is given every three hours for twenty-four hours and then every two hours for twenty-four hours, occasionally for forty-eight hours. Normal rhythm will usually be established with the above procedure. Anderson[35] stated that 96 per cent of the cases will be restored to normal rhythm if quinidine is added to the postoperative treatment where auricular fibrillation is present. He also noted that auricular flutter was noted only three times, and in two cases alternately with fibrillation; two of these cases returned to normal rhythm with the use of quinidine sulfate.

If signs of cardiac decompensation make themselves manifest, digitalis is the drug of choice. The percentage of cases in which the heart rhythm returns to normal after thyroidectomy depends chiefly on the duration of the irregularity of the heart rhythm prior to operation, the degree of arteriosclerosis and myocardial degeneration, the age of the patient, and complications such as focal infections.

Lugol's solution should be given after the first postoperative day in doses of 5 to 10 minims (.31 to .62 cc.) three times daily while the patient is in the hospital. The average dose in this clinic is 8 minims (.48 cc.) three times a day. The first postoperative day is taken care of by the 30 minims (1.85 cc.) given in the enteroclysis. In very mild toxic cases, iodine may be omitted entirely postoperatively but will do no harm. Davison and Aries[49] claim that if sufficient gland has been removed and if the patient has been prepared adequately preoperatively, the use of postoperative iodine has no rational basis. They studied a series of 100 cases in which fifty of them had been given iodine postoperatively and fifty had been given no iodine. Those patients in whom no iodine had been given had milder reactions. It is definitely indicated, however, in such incomplete operations as polar ligations, lobectomy and the removal of discrete adenomas and in all cases in which there has been residual thyroid tissue left behind, necessitating protective iodinization. If the operation has been successful, iodine need not be given after the patient is discharged from the hospital.

Postoperative hemorrhage demands immediate attention or it may prove fatal. The immediate separation of the wound and expression of the clots may be necessary in the massive type to prevent suffocation. Concealed hemorrhage should be taken care of early before symptoms become severe. The patient is taken back to the operating room, the wound opened, clots expressed and the bleeding point ligated with accuracy.

Serum pockets, if large, should be drained and if very small, they may be absorbed without any treatment. If a drain has been used, it should be removed in twenty-four hours. The strictest asepsis should be used in dressing all goiter wounds because infection is borne poorly by these patients.

The basal metabolic rate is taken before the patient leaves the hospital and in three months after discharge to determine whether or not any hyperthyroidism or hypothyroidism is present. If these are suspected, the patient should return for observation and the institution of proper medical treatment.

Postoperative laryngoscopy should be performed to determine the condition of the larynx before the patient leaves the hospital. This examination, together with the one done preoperatively, will often determine whether a voice difficulty was due to operative injury or whether the difficulty is a transient or a permanent one.

The subject of thyroid crisis should receive some attention; although uncommon today, it still occurs. Pemberton[50] stated that perhaps in every operation for active goiter some reaction of hyperthyroidism occurs. When the patient has been properly prepared preoperatively this reaction is so mild that clinically it can scarcely be distinguished from the normal postoperative response and it differs only in increased sweating, a moderate rise in temperature and pulse rate and perhaps in the development of intermittent irregularity of cardiac rhythm. These symptoms as a rule do not develop until six to twelve hours or even longer and usually subside within twenty-four to forty-eight hours without materially influencing the patient's convalescence. The more severe hyperthyroid reactions differ only from the typical crisis of the pre-iodine period in that they are not accompanied by the extreme mental agitation, the restlessness and the general toxic state as previously seen. The treatment of crisis consists of oxygen therapy, ice

bags, sedatives (morphine in the more severe cases) and intravenous glucose and fluids. Iodine in large doses may be decidedly helpful. The best treatment, however, is preventative, that is, adequate preoperative preparation.

Maddock, Pederson and Coller[51] stated that with further knowledge of the cause of thyroid crisis, specific measures may be possible to avoid this serious complication.

Delirium and confusion may follow thyroidectomy. It usually occurs in patients more than sixty years of age, who are emaciated, feeble and have had hyperthyroidism for several years. Dinsmore and Crile[52] claim that confusion can usually be demonstrated to be the result of liver failure, kidney failure, the cumulative effect of some drug or an unclassified type of metabolic exhaustion. The treatment of these conditions is the administration of glucose.

Exophthalmos is usually expected to decrease after thyroidectomy or to disappear entirely. Often the ocular changes are very slow in improving, gradual recession taking place many months after operation. In the more severe cases exophthalmos may remain permanently. Zimmerman[53] stated that in eight cases of hyperthyroidism, exophthalmos developed after the operation. There is no definite explanation for this phenomenon. Malignant or progressive exophthalmos may also occur and is a very unfortunate thing to have happen. Most patients that develop this are in a hypothyroid state. Treatment is difficult and operations have been designed for this condition but are not always successful.

Tetany is a harassing thing for the surgeon if it occurs postoperatively. The best treatment is again prevention, that is, the protection of the parathyroids from actual removal or trauma during operation. If they are removed, they should be transplanted immediately. No cases of tetany were seen in the cases reported.

If active tetany occurs, parathormone should be given during the acute stage with calcium salts by mouth or intravenously. Clifton[54] believes that the chronic cases should be given a high carbohydrate diet with calcium in large doses. Eppinger and Levine[55] found tetany to be an infrequent complication following total thyroidectomy. They recommended 5 to 10 minims (.31 to .62 cc.) of viosterol and 4 to 8 Gm. (approximately 60 to 120 gr.) of calcium lactate daily for a period of from two to three weeks, and in no instance was parathyroid extract needed. Guthrie and Brown[56] reported in 1939 the absence of permanent tetany in over 4,100 cases.

The diet following thyroidectomy is relatively simple. The patient is allowed liquids as soon as tolerated except stimulants such as coffee or tea. On the third day a modified soft diet which consists of toast, jello, etc., should be allowed. Following this a soft diet is given. This consists of everything except meat. The regular house diet which should be of a high carbohydrate content is well tolerated by the patient on the fifth or sixth day. The soreness of the throat which is prevalent in the first few days should have subsided by this time. Of course, postoperative nausea and vomiting may modify this régime to a certain degree and each individual case will have to be dealt with accordingly. Associated conditions such as diabetes mellitus should receive their special diets as determined by frequent blood sugars. These diets are covered with insulin according to the needs of the patient.

The care of the bowels is important. Milk of magnesia in doses of 1½ ounces (45 cc.) is given on the second or third day if necessary; liquid cascara, drachms 1, (4 cc.) is equally effectual and perhaps better in many cases. A saline enema may be required if postoperative distention occurs. The normal bowel habits of the patient should be instituted as soon as possible.

Associated diseases are treated just the same as if the thyroid condition had not entered the picture. A marked reduction

in many cases of hypertension is noted without any further treatment. Symptoms which have been diagnosed as other diseases may often disappear. This is especially true of vague abdominal symptoms. Since the thyroid is so intimately connected with the endocrine chain, it is easily understood why these symptoms are either relieved or abated entirely.

The chair is allowed on the fourth postoperative day if the convalescence up to this time has been uneventful. Walking is allowed on the fifth day, usually just bathroom privileges. After this, the patients are allowed gradually to increase the walking each day but they are kept on limited activity the entire postoperative period and are advised to continue the same after going home.

The average time for discharge in this clinic is ten days, however, this varies considerable depending on the postoperative course. Those patients who show marked signs of cardiac damage and severe hyperthyroidism may be advised to stay for a much longer period of time. Experience of the medical staff should be allowed to control this factor as well as guide most of the postoperative care. Guthrie[57] pointed out that the older patient who shows the effect of prolonged and severe toxemia should have long periods of rest under strict and intelligent medical supervision but the younger patient who has no symptoms of vascular, hepatic or renal damage may be returned to partial activity soon after their arrival home. These patients should be advised to return if any questions as to their well being arises, and it is well to keep in touch with them for at least one year, or longer if necessary. This is not only for the good of the patient but it will also act as a gauge for the thyroid team to determine whether or not their treatment has been successful. In many cases it is gratifying to both the surgeon and internist to see these patients being returned to society normal individuals.

## ANALYSIS OF CASES REVIEWED

The preoperative and postoperative treatment as given in this paper is not only derived from the voluminous literature on the subject but also on the analysis of 100 cases treated in the Guthrie Clinic. These were taken from the records of 1938 and 1939, and represent the typical cases taken care of in this clinic. Cases representing all degrees of toxicity are included in this series and it might be interesting to note that there was no mortality. This analysis will be given in the following paragraphs to bear out the statements already made. Certain details of laboratory findings and signs not already mentioned will also be discussed such as blood and urine studies.

This series represented forty-nine cases of primary hyperthyroidism and fifty-one cases of toxic adenomatous goiter. This near equality of cases should give a relatively concise cross section of the same. There were ninety-one females and nine males ranging in ages from nineteen to seventy years, the average age being forty-seven years. A subtotal thyroidectomy was performed on each of these patients. The amount of tissue allowed to remain was judged by the experience of the surgeon and degree of toxicity. It varied from one-fourth to one-eighth of the gland. Silk technic was used throughout, drains were placed in three cases, every wound healed by primary intention and serum pockets formed in only eighteen cases. The sternohyoid muscle was divided in thirty-one cases to form a unilateral trap door and in ten cases to form a bilateral trap door. Fifty-nine cases required no trap door. This was done for safety in removing the gland. The general condition of the patient during the operation was considered good except in two cases and these two were classified as fairly good. The average time of operation was fifty-eight minutes, however, this should not be stressed as important because haste is not necessary with a well prepared patient.

Adequate time should be taken to secure hemostasis and safeguard the many vital structures such as parathyroids, recurrent laryngeal nerves, trachea and the great vessels of the neck.

On admission many of these patients showed some degree of fever, the highest being 104.3°F. in a patient admitted with bronchopneumonia. This was controlled by sulfapyridine. The average pulse rate was 105, which dropped to 88 after adequate treatment. During the operation the average pulse was 120. The peak following operation was 114 which gradually declined to 80 at the time of discharge. These averages give a very clear picture of what happens in the average case.

The number of days required for preparation was eleven, the maximum number being 30. This short length of time of preparatory treatment may be influenced by the fact that a few of the patients were treated at home and came well prepared. The average postoperative days were ten, the maximum being eighteen. The reason for this extended hospital stay postoperatively was due to a second operation, the excision of a lipoma. The patients were usually gotten out of bed on the fourth day.

Iodine was administered preoperatively in the form of Lugol's solution, the average dose being minims 15 (.92 cc.) three times a day. This also varied from minims 10 to minims 20 (.62 to 1.23 cc.) depending, of course, upon the toxicity of the case. Thirty minims (1.85 cc.) of Lugol's solution was given immediately after operation in the first 1,000 cc. of proctoclysis. On the second day Lugol's solution, minims 8 (.48 cc.) three times a day, was the average dose, this amount varied also depending upon the needs of the patient and in most cases was continued until the patient left the hospital. No iodine was advised after the patient left the hospital.

The blood picture was not unusual except the presence of a mild secondary anemia. The hemoglobin estimations showed an average of 75 per cent and red blood cells 4,089,000. The white blood cells were essentially normal, the average being 6,573, of which 63 per cent were polymorphonuclear cells and the remaining 37 per cent were small lymphocytes. An occasional case showed a slight eosinophilia.

The average blood cholesterol reading was 150 mg. per 100 cc. of blood; this was within the lower limits of normal which ranges from 140 to 200 mg. The lowest cholesterol readings were 96, these being in very toxic cases.

The blood urea nitrogen was 15 mg. per 100 cc. while the fasting blood sugar average was 97 mg. per 100 cc. of blood. These readings were of no particular significance except to show that the kidneys were eliminating waste products properly and to show the presence or absence of diabetes. There were several cases of diabetes but these were well controlled by diet and insulin.

The Kahn test was the predominant one used to show the presence or absence of syphilis. It was positive in two cases and in one of these a Wassermann was done which was negative. Syphilis is not as prevalent in this section of the country as it is in urban areas.

The routine urine examination showed an average specific gravity of 1.016. A number of cases showed some albumen and those with diabetes mellitus varying amounts of sugar.

Since there were so many factors that influence the metabolic rate it is almost impossible to give accurate figures. An attempt was made to analyze the rate in this series and it was found that the average metabolic rate on admission was plus 42. This figure was reduced to plus 32 before operation under appropriate treatment and just before discharge the rate had dropped to plus 12. These figures probably do not agree exactly with other clinics, but they do show that the drop sought for had been obtained.

Weight gain is one important criteria of a successful thyroid treatment regimen. From the time of admission for the treatment until the routine check-up, the

average weight gain in seventy-seven of the 100 cases was twelve pounds. Since twenty patients did not return for a check-up and in three the weight records were not complete, the average was taken for the seventy-seven cases.

The anoci-association technic was carried out in eighty-eight cases. The average dose of sodium amytal given was 6 gr. (.396 Gm.) while several received but 3 gr. (.198 Gm.). The usual preoperative hypodermic of morphine sulfate 1/6 (.011 Gm.) and atropine sulfate gr. 1/100 or 1/150 (.00066 or .00044 Gm.) was used in all the cases except two. In one of these cases amytal gr. 3 (.198 Gm.) was used instead of the preoperative hypodermic and in the other case codein gr. 1 (.066 Gm.) was substituted for morphine. No reason was given for the first but the latter case could not tolerate morphine.

Ethylene anesthesia was used exclusively. The usual ethylene-oxygen ratio is 80 to 20 but cases of extreme toxicity required a higher percentage of oxygen. Before the anesthetic was started, the anesthetist was advised as to the relative toxicity of the patient so that the ethylene-oxygen mixture could be arranged accordingly.

Thyroidectomy showed a decided beneficial effect on nine cases of hypertension. According to Hurxthal[58] the pulse pressure is increased in hyperthyroidism and decreased in about 50 per cent of the patients following relief from thyroid toxicity. Generally speaking this was true in our series of cases in which the blood pressure was studied and especially true in these nine cases of hypertension.

In reviewing the postoperative complications, heart irregularity was the most common. This should really not be classified as a complication because many of the cases showed considerable cardiac damage before operation. In several of the cases, fibrillation did not present itself until the second or third postoperative day. This fibrillation did not always require medication because it cleared up spontaneously within a short period of time. In the more severe cases of fibrillation, quinidine was used with excellent results. One patient who had been seen in the clinic many times with severe cardiac damage died three months after discharge; this was presumably a cardiac death. Quinidine, digifolin and digitalis had been used on this case at various times. Two patients developed postoperative hypothyroidism, one with a basal metabolic rate of minus 22. There was one case of pleurisy, one toxic psychosis, one pulmonary atelectasis of the left lower lobe of the lung, one acute pyelitis, and one pulmonary infarct. These patients all recovered. One patient showed some infection of the wound about one month after discharge which cleared up after several suture knots were removed. No cases of thyroid crisis were noted in this series. The benefits that most of these patients derived from their thyroidectomy far out-weighed any of the complications that arose except the one who died three months after being discharged from the hospital. This patient probably received no gross benefit from the treatment.

All the patients were advised to return for a routine check-up, the average time being about six weeks. Many were told to return much sooner, especially if it was thought advisable because of individual circumstances. Out of the 100 cases, eighty returned and twenty did not. The results were generally good in all but three; one of these had arteriosclerotic heart disease, the second had hypothyroidism and when given thyroid extract showed improvement, and the third had hypertensive heart disease, questionable lues and calcification of the aortic arch.

An attempt has been made to discuss fully the general trend and ideas of treatment as set forth in the voluminous literature on the subject of the preoperative and postoperative treatment of the toxic thyroid. In order to further substantiate these data, 100 typical cases from the Guthrie Clinic have been re-

viewed and the information gained has been discussed.

## CONCLUSIONS

The evolution of the treatment of toxic goiter has extended over many centuries. This treatment has had a more rational basis since more is understood of the physiology and chemistry of the thyroid gland.

The general practitioner, as well as the clinic, play a very important rôle in the early treatment of this condition.

Scientific preoperative iodine therapy is the most important phase in the presurgical treatment. Its value postoperatively is without question.

The laboratory is so closely linked, with both diagnosis and treatment of the toxic thyroid, that its value should not be lost sight of throughout the entire course of the disease, preoperatively, surgically, and postoperatively.

Associated diseases require the same careful preparation as does the diseased thyroid.

Anoci-association is of distinct advantage in keeping the patient in that state of restfulness which is so much desired at the time of operation.

Ethylene anesthesia is the anesthetic of choice.

The well prepared patient will be one whose major symptoms have subsided, whose confidence is irreproachable, and in the minds of both surgeon and internist is a safe operative risk.

One stage subtotal thyroidectomies should be performed wherever possible, and only in the most severe cases should a two-stage operation be advised.

Non-absorbable suture material, silk or cotton, is preferable to catgut.

The oxygen tent is a valuable aid in relieving respiratory or circulatory embarrassment.

Postoperative hemorrhage is a serious complication and must receive immediate attention.

Some cases of hypertension associated with hyperthyroidism receive definite benefit from thyroidectomy.

Each patient, being treated for hyperthyroidism, must be considered a definite problem of individualism in the preoperative and postoperative treatment.

The analysis of 100 cases have been presented to substantiate these facts.

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# THE EFFECTS OF PYRIDIUM IN CERTAIN UROGENITAL INFECTIONS*

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IN 1940, Morrissey and Spinelli[1] published a report on the clinical employment of pyridium, in which they stressed its beneficial analgesic and anesthetic effects on the urogenital mucosa. During the course of their study, they noted a reduction of from one-half to two-thirds of the amount of urinary sediment in surgical cases receiving pyridium. Pointing out that this portion of the study had been somewhat limited, they suggested a further investigation of this effect of pyridium.

In 1941, Braitberg[2] published the results of such an investigation. In this study, 80 per cent of the cases of urinary tract infections treated with pyridium showed a 50 per cent or more decrease in organized urinary sediment. With very few exceptions, a reduction of urinary sediment was accompanied by a decrease or disappearance of the subjective symptoms.

The purposes of the present study are: (1) to confirm the limited observations made by Morrissey and Spinelli on this effect of pyridium, and (2) to confirm and extend Braitberg's findings, with special reference to correlating the effect of pyridium in reducing the organized urinary sediment and its well known action of relieving the distressing symptoms of urinary tract infection.

## HISTORY OF DRUG

Pyridium is the brand name for phenyl-azo-$\alpha$-$\alpha$-diamino-pyridine monohydrochloride. This azo dye first came into general clinical use among American urologists toward the end of the 1920's. Upon its original introduction, special stress was placed upon its marked powers of tissue penetration. Thus, as early as 1927, Belfield and Rolnick,[3] Chicago urologists, had noted that on microscopic examination of spermatic fluid ejaculated by a patient under treatment with pyridium, the heads of the spermatozoa were stained with a yellow coloration characteristically produced by this drug. This was an emphatic confirmation of the claims of powerful penetrative action.

No attempt will be made here to review all of the many published reports on the clinical use of pyridium in urogenital infections. By 1934, clinical reports thereon had been made by urologists so often that Walther and Willoughby[4] undertook a general evaluation of its merits and limitations through a survey of the literature and classification of the accumulated data. Among the many papers cited by these authors was that of Mason,[5] published in 1931. This investigator attested especially to the benefits which patients with prostatitis had received from pyridium therapy, both prior to and following operation, as well as in those cases in which surgical procedures had not been employed.

Most of the authors who have studied the clinical effectiveness of pyridium have made some statement indicating how closely pyridium approaches the "ideal

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antiseptic" for urinary infections—that touchstone so long but *vainly* sought by all who cultivate the special field of urology. No one, so far as we are aware, has ever reached that ideal, but it is an objective of the present contribution to show further progress in that direction.

### EFFECTS OF PYRIDIUM ADMINISTRATION

The beneficial effects of pyridium therapy in urogenital infections are well established. Walther[6] stated that he had found the sphere of usefulness of this type of drug a wide one, because it is equally effective in an acid or an alkaline medium, requires no special dietary regimen, and has a soothing effect on the inflamed mucous membrane. He believes that a large part of the usefulness of this type of drug lies in its capacity to penetrate the tissues and attack the bacteria in their own habitat. Mason's[5] outstanding results following the use of pyridium were obtained in cases of acute, subacute, and chronic prostatitis and also in chronic and subacute pyelitis and pyelonephritis. Freedom from all clinical symptoms, together with results of careful weekly urine analyses, convinced him of the marked benefit obtained from pyridium therapy. Braitberg's[2] work on organized urinary sediments has already been noted.

### BASIS OF THE PRESENT STUDY

The present study is based on a series of 118 cases, all under observation for two weeks or longer. Various types of urinary infection were treated with pyridium, the usual dosage being two tablets of 0.1 Gm. each, administered three times daily. Twenty-four-hour specimens of urine were collected from each patient for several days *before* pyridium therapy was instituted, and the final specimen secured two weeks later, while the patient was being maintained on the pyridium regimen.

At each examination the influence of pyridium in reducing the amount of organized urinary sediment was noted by comparison with previous records; at the same time, careful attention was accorded the characteristic symptoms of urinary infection which the patient exhibited, whether unabated, lessened, or entirely

TABLE I

ANALYSIS OF 118 CASES TREATED WITH PYRIDIUM

| Diagnosis | No. Cases | Frequency | | Dysuria | | Burning | | Nocturia | | Cases Showing Reduction in Sediment |
|---|---|---|---|---|---|---|---|---|---|---|
| | | No. Cases | Improvement | No. Cases | Improvement | No. Cases | Improvement | No. Cases | Improvement | |
| Cystitis and pyelonephritis. | 75 | 70 | 60 (85.7%) | 28 | 27 (96.4%) | 52 | 49 (94.2%) | 54 | 48 (88.8%) | 43 (57.3%) |
| Prostatic hypertrophy. | 14 | 13 | 12 (92.3%) | 4 | 4 (100.0%) | 6 | 6 (100.0%) | 14 | 11 (78.6%) | 8 (57.1%) |
| Postoperative: Following resection of prostate (carcinoma). | 18 | 17 | 15 (88.2%) | 8 | 7 (87.5%) | 12 | 11 (91.6%) | 16 | 13 (81.2%) | 11 (61.1%) |
| Urethritis..... | 9 | 9 | 6 (66.6%) | 2 | 2 (100.0%) | 8 | 7 (87.5%) | 6 | 3 (50.0%) | 1 (11.1%) |
| Diverticulitis*..... | 2 | 2 | 2 (100.0%) | 1 | 1 (100.0%) | 1 | 1 (100.0%) | 2 | 2 (100.0%) | 2 (100.0%) |
| Total No. cases..... | 118 | 111 | 95 | 43 | 41 | 79 | 74 | 92 | 77 | 65 |
| Average per cent of improvement..... | ... | ... | 85.6% | .. | 95.3% | .. | 93.6% | .. | 83.7% | 55.1% |

* This is obviously not a significant number of cases. They are included merely to complete the series.

abolished. A summary of our observations appears in Table 1.

These results support the observations of Morrissey and Spinelli[1] and of Braitberg.[2] They also are in accord with the findings of Reynolds, Wilkey, and Choy,[7] as well as those of many other investigators who have observed the effectiveness of pyridium in relieving the characteristic symptoms of urinary infection.

### DEFINITION OF ORGANIZED SEDIMENT

In speaking of "organized sediment," granular, epithelial, blood and other pathologic casts have been excluded. The unorganized sediment (salts) was excluded because its presence in the voided urine depends upon many factors unrelated to urinary tract infection, such as diet, hydrogen-ion concentration, enzyme action, or temperature changes affecting collected urine.

### METHOD OF SECURING SPECIMENS

In securing the specimens we used Goetz phosphorus centrifuge bottles, 100 cc. volume, with 1 cc. tip capacity, which were calibrated in .05 cc. graduations. Four-liter brown specimen bottles were employed, 5 cc. of a 10 per cent solution of thymol being placed in each bottle before the urine was added.

### DETERMINATION OF AMOUNT OF SEDIMENT

The following standardized technic was carried out in estimating the total amount of organized urinary sediment:

1. Shake bottle containing twenty-four hour specimen vigorously until sediment is evenly distributed.

2. Immediately pour 150 to 200 cc. into a beaker.

3. While gently stirring, add 10 per cent hydrochloric acid, drop by drop until hydrogen ion concentration is 5.5. Nitrazine paper SPOT test.

4. Add the urine at hydrogen ion concentration 5.5 to the 100 cc. centrifuge bottle, and pour the remainder back into the twenty-four-hour specimen bottle.

5. Measure the volume of urine from specimen bottle into a 100 or 200 cc. graduate; add 100 cc. for that used in sample for analysis.

6. Place centrifuge bottle in the proper holder and centrifuge for fifteen minutes at the rate of 1,800 revolutions per minute.

7. Record sediment percentage and volume. The total organized sediment will equal the volume times the sediment percentage over 100.

$$\frac{\text{Volume} \times \text{Sediment Percentage}}{100} = \text{Total Organized Sediment}$$

### COMMENTS

The patients were divided into four groups. In Group 1 there were twenty-nine patients who complained of such symptoms as frequency, urgency, burning, and intermittent pain. They were almost equally divided as to sex, fifteen being females and fourteen males. Duration of symptoms prior to the administration of pyridium varied all the way from "a few days" to "several years," "several months" being the period most frequently reported on the history charts.

Of this entire first group, only two patients were reported as receiving no benefit whatever from the medication. In practically every case in which dysuria had been a common symptom, the pain either disappeared completely or was greatly reduced following the course of pyridium therapy. In most cases in which frequency and nocturia were originally the chief complaints, once treatment with pyridium was instituted the intervals between bladder evacuations were lengthened, and sleep became possible without interruption in all but a few exceptions.

In this group, reduction of the organized urinary sediment was equally striking. In one case of chronic pyelonephritis and cystitis, not only was there complete relief of symptoms, but the amount of urinary sediment fell from 0.18 cc. per 100 cc. of

urine at the beginning of treatment, to .05 cc. after two weeks of pyridium therapy. In another case, the total sediment fell from 0.15 cc. per 100 cc. of urine to .06 cc. In a number of cases, the amount of organized urinary sediment remained practically constant, although in these cases also there was marked symptomatic improvement.

Group II was made up of thirty patients, most of whom were hospitalized for such serious urologic conditions as renal calculus, prostatic hypertrophy, carcinoma, chronic cystitis, and pyelonephritis. Although this group contained a majority of females, some of the most striking results occurred in males with prostatitis, especially those whose infections occurred postoperatively. In the case of two female patients, no improvement was noted after a full course of pyridium, and in general, results were not so good in this group as in Group I. It should be noted, however, that the pathologic conditions in the patients which comprised this group were of much longer standing and were associated with more profound systemic disturbances than prevailed in the first group.

Group III contained thirty-five patients, twenty-five of whom were females. The urogenital conditions in this group also were more severe and of greater duration than those in Group I. One patient, a man of seventy-five years, suffered with an inoperable carcinoma of the prostate and urinary infection of several years' standing, complicated by a serious cardiovascular syndrome. Nevertheless, even in this undeniably hopeless condition, regular pyridium administration reduced the urinary sediment from .06 cc. per 100 cc. of urine to .04 cc., while the general condition showed far more improvement than the statistical results reported in the accompanying table would indicate. Another patient, a man of sixty-seven years, with acute pyelonephritis and uremia of several weeks' duration, had a total daily urine output of but 700 cc. at the beginning of treatment, with sediment of 0.12 cc. per 100 cc. After the two weeks' course of treatment, the twenty-four-hour urinary output increased to 1,600 cc., whereas the total organized urinary sediment fell to .04 cc. per 100 cc. In a woman, age thirty-eight, with cystitis, the volume of urine fell from 1,500 cc. to 1,200 cc., but the amount of urinary sediment likewise declined from .06 cc. to .03 cc. per 100 cc. In but one case in this group was there a significant increase in urinary sediment, with a comparative lack of improvement in the associated symptoms. A small number of patients in this group showed no significant improvement following the regular course of this medication.

Group IV consisted of twenty-four patients, whose conditions were largely postoperative, and with the exception of one young woman, age twenty-four years, the patients were all of advanced age. In this group the least objective benefit appears to have been obtained from pyridium therapy, for there was a marked reduction in the amount of urinary sediment in but four cases. The reasons for this lack of response to measures which had proved so beneficial in the first three groups seem to us to be entirely apparent in the nature of the cases, which were for the most part long-standing, neglected urinary infections in patients of advanced age and general lack of resistance.

## CASE REPORTS

The following case histories have been selected as representative of the various groups discussed:

Group I. C. S., female, age thirty-four, complained of frequency and urgency of several weeks' duration, with burning on urination. At the time of admission, the volume of urine varied from 1,500 to 1,600 cc. and the urinary sediment varied from 3 to 0.18 cc. per 100 cc. Diagnosis was right renal calculus with right-sided pyelonephritis and cystitis. The patient was placed on the pyridium regimen consisting of two tablets of 0.1 Gm. each, three times daily. At the end of the first day of pyridium therapy, the volume of urine de-

creased to 1,260 cc., with urinary sediment of 4 cc. per 100 cc. The following day the volume was reduced still further to 820 cc., with the percentage of sediment remaining unchanged. Thereafter improvement was steady, so that on the fourteenth day volume of urine had reached 1,850 cc. whereas the urinary sediment was reduced to 1 cc. per 100 cc. Relief of symptoms was complete.

Group II. A. M., female, age seventy-six, complained of frequency and burning on urination. This patient had been obliged to arise two or three times during the night, intermittently for several months. The tentative diagnosis was cystitis and the patient was placed on the regimen of two pyridium tablets of 0.1 Gm. each, three times daily. On admission, the urinary volume was 1,630 cc. and the sediment percentage 18. The second day following admission, the urinary volume was 1,600 cc. and the sediment percentage only 2. However, on the third day, with the volume at 1,700 cc., the sediment again was 18 per cent. This setback proved to be only temporary, however, for by the fourteenth day, even though the volume had increased to 1,900 cc., the sediment was down to 3 per cent. Furthermore, the patient was able to retain urine for three or four hours during the day, and was compelled to arise only occasionally during the night.

Group III. C. G., female, age fifty-nine, had suffered for two years with dysuria, frequency, and nocturia. There was sharp pain on urination, followed by burning, and she was obliged to arise six or seven times during the night. The diagnosis was chronic pyelonephritis, cystitis, and stricture of the urethra. On admission, the volume of urine was 1,100 to 1,200 cc., and the sediment was .04 cc. to .06 cc. per 100 cc. Routine pyridium therapy was instituted after a preliminary trial of sulfathiazole had been made without benefit.

Because of clinical remission of symptoms, pyridium therapy was suspended, after which all the original symptoms promptly recurred. These were again controlled with pyridium therapy. On the fourteenth day, the intervals between urination had increased from one hour on admission to four or five hours. All pain and burning had ceased, although the patient was still obliged to arise once, or sometimes twice, during the night. The volume of urine remained practically unchanged, but the organized urinary sediment fell to .03 cc. per 100 cc.

Group IV. C. O'C., age eighty-three, had undergone transurethral resection for carcinoma of the prostate. His chief postoperative complaints were frequency, sharp pain and burning during micturition, and the necessity of arising two or three times at night to urinate, which constituted a severe strain on this patient's physical condition. On the first day of pyridium therapy, the urinary volume was 1,800 cc., but the following day it fell to 1,600 cc. Urinary sediment remained at 0.6 cc. per 100 cc. throughout. Fourteen days after pyridium therapy had been instituted, this elderly patient was able to retain urine from three to five hours, no pain was experienced when urinating, and he was forced to arise not more than twice, and often only once, during the night. Although the urinary volume subsequently rose to 2,000 cc., urinary sediment was only 3 per cent.

## TOXICITY

Recent developments in the field of chemotherapy have focused merited attention on the too often neglected question of drug toxicity. With this in mind, each patient receiving pyridium was carefully questioned and observed for evidence of any toxic effects attributable to this drug. Without exception, no toxic effects were observed. From these observations it appears that pyridium may be administered in therapeutic dosage with complete confidence in its safety and lack of toxic effects throughout the usual course of urinary infections.

## SUMMARY

A study was made of 118 cases of urogenital infections. Routine pyridium therapy administered for a period of two weeks resulted in a significant reduction of the organized sediment in sixty-five, or 55.1 per cent of the cases, together with relief of the characteristic symptoms of urogenital infection. In the remaining fifty-three cases, relief of symptoms occurred in all but a few exceptions, although there was no concomitant reduction in the organized urinary sediment.

Relief of the distressing symptoms characteristic of urogenital infections occurred

as follows: Pain on urination was alleviated or abolished in 95.3 per cent of the cases; burning on urination was relieved in 93.6 per cent of the cases; the intervals between bladder evacuations became normal or were greatly extended in 85 per cent of the cases; and nocturia was eliminated or reduced in 83.7 per cent of the cases.

Careful observation revealed no toxic effects from routine administration of this drug, in the dosage of two tablets (0.1 Gm. each) three times per day, throughout a minimum period of two weeks.

## CONCLUSIONS

Pyridium has proved to be a valuable addition to the physician's weapons against infections of the urinary tract.

In a significant number of cases, it has been found to be effective in reducing the amount of organized urinary sediment, and especially in relieving the characteristic symptoms of urogenital infections, such as dysuria, burning, frequency, and nocturia.

Relief of symptoms occurred in most instances even when no decrease in the amount of organized urinary sediment was observed.

Pyridium may be administered in therapeutic dosage with complete safety throughout the course of common urogenital infections.

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# PROGNOSIS IN PROLONGED UNCONSCIOUSNESS FOLLOWING HEAD INJURY*

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UNCONSCIOUSNESS which persists for a period of days in a patient who has suffered a severe craniocerebral injury is a source of anxiety to the family and friends of the individual, and of perplexity to the attending physician. Most neurosurgeons have had a sufficient experience with such cases as to have formed an impression of the outlook, but in a general hospital the resident staff as well as the family physician or surgeon are beset by doubts both as to the proper care of such patients and as to what prognostic assurance they may legitimately give the family. This is particularly true when the neurosurgical consultant cannot always be immediately available, as is frequently the case. Singularly enough little information is available either in textbooks or in the literature. The purpose of this paper is to lay the groundwork for a scientific clarification of this situation.

Any problem involving a discussion of the unconscious state necessarily requires a definition of the sense in which the term is used, since it is loosely applied to a wide variety of conditions ranging from profound coma to mild delirium or stupor. For the purposes of this paper a patient will be considered to be unconscious when he appears neither to have knowledge of his surroundings nor to perceive the stimuli which are directed at him. This concept is based on the opinion of Mapother (1937) that "the only practicable criterion of 'recovery of consciousness' is awareness of external environment and accessibility." When a patient attains this level, he falls into a group which is well recognized by everyone, since a moderate degree of post-traumatic amnesia and stupor are commonly seen sequelae of even relatively mild craniocerebral injuries. Therefore, a less strict interpretation of the meaning of unconsciousness, while it would provide a larger number of cases to report, would also mean the inclusion of cases in which the same therapeutic problems and the same concern do not obtain, and accordingly is not employed.

It is well known that by far the greater proportion of deaths among cases of craniocerebral injury occur in the first twenty-four hours and that the majority take place in less than 72 hours. These facts are amply demonstrated by the survey made by Courville (1937) of 919 cases of injury to the brain and its envelopes coming to autopsy in the Los Angeles County Coroner's Department. His figures indicate that approximately 70 per cent of the deaths occurred in the first twenty-four hours plus an additional 10 per cent in the next forty-eight hours. The remaining 20 per cent were spread over a period of weeks. Of course, this series included a number of deaths occurring at once, a group which does not enter into statistics compiled from hospital admissions. However, Jefferson (1933) has reported a large series of cases among which there were 152 deaths, and of these 119, or 79 per cent, occurred in the first seventy-two hours. Taken all in all the first twenty-four hours is to be regarded as the most critical, the first three days as the relatively critical period. Thereafter the mortality is only 3 to 4 per cent (Jefferson, 1933; Swift and Berens, 1938).

It is likewise true that the greater proportion of patients with craniocerebral injuries recover consciousness in the first

* From the Department of Surgery, The Union Memorial Hospital, Baltimore.

twenty-four hours. Russell (1932) reported that 137 or 69 per cent of 200 patients with head injuries regained consciousness within twenty-four hours, and the figures of Eden and Turner (1941) are comparable. However, it is the group of patients who remain unconscious for longer than the seventy-two-hour critical period with whom this study is concerned, and it will be shown that they constitute the greater proportion of those patients who do not regain consciousness in the first twenty-four hours.

Table 1

| Period of Unconsciousness | No. of Cases | | Deaths | Mortality, Per Cent |
|---|---|---|---|---|
| Less than 24 hours..... | 181 | 81% | 13 | 7½ |
| 24 to 48 hours..... | 10 | 4½% | 7 | 70 |
| 48 to 72 hours..... | 3 | 1½% | 2 | 67 |
| Greater than 72 hours... | 30 | 13% | 5 | 17 |

Table 1. The 224 cases of craniocerebral injury studied are grouped according to the duration of the period of unconsciousness. The number of deaths in each group together with the mortality rate is given.

## RESULTS

For the purposes of this paper a survey of all the cases of head injury admitted to the Union Memorial Hospital from January 1, 1937, to March 31, 1942, was made. These numbered 261. Of these thirty-seven had given no history of unconsciousness nor of retrograde or post-traumatic amnesia and were obviously of such a trivial nature as to justify their elimination from any series of craniocerebral injuries on the same grounds that Coleman excluded 143 of the 596 cases he reported in 1931. Among the remaining 224 patients of the present series 181 were unconscious less than twenty-four hours, ten from twenty-four to forty-eight hours, three from forty-eight to seventy-two hours, and thirty for periods greater than seventy-two hours. (Table 1.) Divided according to the method of Munro (1936) into non-operable, operable, and complicated groups, 196 fell into the first, twenty into the second, and eight into the third, with respective mortality rate of 7½, 50, and 25 per cent. There were twenty-seven deaths (12 per cent) for the whole series of 224 cases. (Table II.)

For the thirty patients in whom unconsciousness persisted longer than seventy-two hours the general mortality was 17 per cent. Among these thirty cases twenty-one were non-operable, six operable and three complicated. The mortality rates were 9½, 33, and 33 per cent, respectively. (Table II.)

Of the twenty-seven fatalities 78 per cent died in the first seventy-two hours, eight dying in the first twenty-four hours, nine in the second, and four in the third. Four died after this period but in less than one week, and two after one week. Twenty-two

TABLE II

| | Total Cases | | | Non-operable | | | Operable | | | Complicated | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No. | Deaths | Mort., Per Cent | No. | Deaths | Mort., Per Cent | No. | Deaths | Mort., Per Cent | No. | Deaths | Mort., Per Cent |
| All cases.... | 224 | 27 | 12 | 196 | 15 | 7½ | 20 | 10 | 50 | 8 | 2 | 25 |
| Cases of prolonged unconsciousness..... | 30 | 5 | 17 | 21 | 2 | 9½ | 6 | 2 | 33 | 3 | 1 | 33 |

Table II. The mortality for 224 cases of craniocerebral injury and the 30 cases of prolonged unconsciousness found among them is shown. They are divided into *non-operable, operable,* and *complicated* groups, according to the method of Munro, and the mortality for each group given.

died without ever recovering consciousness, and of these eight died in the first twenty-four hours, seven in the second, two in the third, three after seventy-two hours but in less than one week, and two after one week. (Table III.)

TABLE III

| | Deaths without Recovery of Consciousness | Deaths after Recovery of Consciousness | All Cases | | |
|---|---|---|---|---|---|
| | | | Deaths | Per Cent | |
| Less than 24 hours | 8 | 0 | 8 | 30 | 78 |
| 24 to 48 hours | 7 | 2 | 9 | 33 | |
| 48 to 72 hours | 2 | 2 | 4 | 15 | |
| 72 hours to 1 week | 3 | 1 | 4 | 15 | |
| After one week | 2 | 0 | 2 | 7 | |
| Totals | 22 | 5 | 27 | | |

Table III. The 27 deaths among 224 cases of craniocerebral injury are grouped according to whether or not consciousness was regained before death and according to the lapse of time between injury and death.

Two hundred two or 90 per cent of the patients studied regained consciousness eventually, although five of these patients later died. Forty-three patients were still unconscious at the end of twenty-four hours of whom seven died and three recovered consciousness during the subsequent twenty-four hours. Of the remaining thirty-three who had not regained consciousness after forty-eight hours two were dead and one had recovered consciousness at the end of seventy-two hours, leaving thirty still unconscious. Three of these patients died within the first week and fifteen recovered consciousness, while two of the twelve patients who were unconscious more than one week died and ten recovered. That is to say, twenty-nine or 68 per cent of those patients still unconscious after twenty-four hours, twenty-six or 79 per cent of those still unconscious after forty-eight hours, and twenty-five or 83 per cent of those still unconscious after seventy-two hours eventually recovered. (Table IV.)

The thirty patients in whom unconsciousness was prolonged for greater than seventy-two hours were studied in more detail. Their average age was thirty-two years (twenty-eight for the non-operable, forty-four for the operable, and thirty-seven for the complicated group). The average age of the patients who died was fifty-six (forty-five, sixty-five and sixty-two, respectively) as compared with

TABLE IV

| Period | Patients Still Unconscious | Died | | | | Recovered Consciousness | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | During Period | | Eventually | | During Period | | Eventually | |
| | | No. | Per Cent | No. | Per Cent | No. | Per Cent | No. | Per Cent |
| Up to 24 hrs | 224 | 8 | 3½ | 27 | 12 | 173* | 78 | 202* | 90 |
| 24–48 hours | 43 | 7 | 17 | 14 | 32 | 3 | 7 | 29 | 68 |
| 48–72 hours | 33 | 2 | 6 | 7 | 21 | 1 | 3 | 26 | 79 |
| 72 hours–1 week | 30 | 3 | 10 | 5 | 17 | 15 | 50 | 25 | 83 |
| After 1 week | 12 | 2 | 17 | 2 | 17 | 10 | 83 | 10 | 83 |

Table IV. The proportion of patients still unconscious at the *beginning* of given periods of time who died or recovered consciousness either during that period or subsequently is shown. It should be noted that many of the patients in the first group were unconscious only a few minutes—also that all the patients who recovered consciousness lived except five in the first group, so that the figures for *recovery of consciousness* also represent *survival* with this exception.

* 5 died subsequently.

twenty-seven (twenty-six, thirty-four and twenty-five, respectively) for the patients who survived. It is striking that in each instance the patients who died were twenty to thirty years older on the average

Table v

| | No. | Average Age | | | Average Hospital Stay, days |
|---|---|---|---|---|---|
| | | Whole Group | Patients Living | Patients Dying | |
| All cases | 30 | 32 | 27 | 56 | 28 |
| Non-operable | 21 | 28 | 26 | 45 | 29 |
| Operable | 6 | 44 | 34 | 65 | 26 |
| Complicated | 3 | 37 | 25 | 62 | 25 |

Table v. The average age and average hospital stay for the thirty cases of prolonged unconsciousness viewed as a whole and divided into *non-operable, operable,* and *complicated* groups are given. The average age of those patients in each group who survived is contrasted with that of those who died.

than those who lived. The average hospital stay was twenty-eight days, twenty-nine for the non-operable, twenty-six for the operable, and twenty-five for the complicated cases. (Table v.)

Twenty-five or 83 per cent of these thirty patients survived; nineteen were non-operable, four operable, and two fell into the group presenting complications. Four of the non-operable patients and one of those with complications had residual mental symptoms. One each of the non-operable and operable groups had neurological residua. This leaves eighteen or 60 per cent who lived and showed no significant residual changes after prolonged unconsciousness following craniocerebral injury. (Table vi.)

## REMARKS

*General Mortality.* In this series of 224 acute craniocerebral injuries there were twenty-seven deaths, a mortality of 12 per cent. This figure is definitely lower than those given by Dandy (1933), Munro (1934), or Coleman (1931) which were 20, 17 to 20.7 and 18.5 per cent, respectively, but is very close to the figure obtained by Swift and Berens (1938) in a study of 1,433 cases in Washington state with a mortality of 13 per cent. It is suggested that the discrepancy may be accounted for by the fact that in a largely private hospital a greater percentage of patients who were unconscious for a short period of time and who have not been very severely injured are admitted for two to four days' observation and rest, whereas they would be followed in the out-patient department in large municipal or teaching hospitals such as those from which the former statistics are reported. This is further reflected in the much lower incidence of operative and complicated cases as compared with Munro's series. One is inclined to wonder, therefore,

TABLE VI

| | No. | Living | | No Significant Residua | | Mental Residua | | Neurological Residua | |
|---|---|---|---|---|---|---|---|---|---|
| | | No. | Per Cent | No. | Per Cent | No. | Per Cent | No. | Per Cent |
| All cases | 30 | 25 | 83 | 18 | 72 | 5* | 20 | 2 | 8 |
| Non-operable | 21 | 19 | 91 | 14 | 74 | 4* | 23 | 1 | 5 |
| Operable | 6 | 4 | 67 | 3 | 75 | .. | .. | 1 | 25 |
| Complicated | 3 | 2 | 67 | 1 | 50 | 1 | 50 | | |

Table vi. The incidence of survival and of mental and neurological residua for the 30 cases of prolonged unconsciousness is given for the whole number and for those cases falling into the *non-operable, operable,* and *complicated* groups considered separately.

* Two over 50.

if such a group as the one herein reported does not more accurately represent the true mortality in cases of craniocerebral injury viewed as a whole.

*Incidence of Prolonged Unconsciousness.* Patients with head injury in whom unconsciousness persists over a period of days are commonly thought to be quite rare. However, Eden and Turner (1941) have recently reported a series of 200 consecutive cases of head injury among which there were thirty-five patients exhibiting post-traumatic amnesia for days and thirteen patients in whom it went on into weeks. The total constitutes 24 per cent of the cases reported. They measure post-traumatic amnesia from the moment of injury to the first return of consecutive consciousness and this less strict interpretation of the unconscious state plus the fact that some of these patients evidently regained consciousness in less than seventy-two hours would tend to make their figure higher than that reported herein.

In the present series thirty or 13 per cent of 224 patients were unconscious for more than seventy-two hours. Even if this figure is not entirely accurate because of the small number of cases, it does indicate that a definitely significant proportion of craniocerebral injuries fall into this group and justifies the undertaking of this study. It is also noteworthy that the greatest number of patients with acute craniocerebral injury recover consciousness within twenty-four hours (81 per cent of this series) and that few of those remaining unconscious after that period respond within the second or even the third twenty-four hours (6 per cent of these 224), while about twice as many go on to prolonged unconsciousness (13 per cent).

*Mortality in Prolonged Unconsciousness.* It might be thought that after a patient gets through the first seventy-two hours following a head injury without regaining consciousness his chances of recovery would temporarily improve, but tend to decline again when the unconscious state persists for many days. This study bears out the first of these assumptions but not the second. Reference to Table IV clearly indicates that the incidence of recovery was not as high among patients still unconscious after twenty-four and forty-eight hours (68 and 79 per cent, respectively) as for patients still unconscious after seventy-two hours (83 per cent). However, it was just as high in patients whose unconsciousness went on for more than a week (83 per cent) as in this last group.

It is impossible to draw conclusions as to the exact percentage of each of these groups which may be expected to recover from such a small number of patients, but it does seem fair to conclude that among patients who do not recover consciousness in the first twenty-four hours the prognosis definitely improves if they get through the first three days, even though they are still unconscious at the end of that time. Thus, in this series the mortality rate was 17 per cent for cases of prolonged unconsciousness as compared with 32 and 21 per cent at the end of twenty-four and forty-eight hours.

It is of interest to note that all but one of the five patients who died after a long period of unconsciousness were over fifty years of age, the average age of patients recovering being twenty-seven as compared with fifty-six for those who died. This is in line with the observations of Martin (1937) and Russell (1932) that patients who suffer a head injury after reaching the age of forty or fifty do poorly. This is true in regard to the amount of residual change as well as in regard to the prognosis for survival, as will be shown.

Russell (1932) has also expressed the opinion that the duration of unconsciousness has little to do with prognosis. This does not seem to be true, at least in regard to the outlook for survival. As is shown in Table I, the mortality for patients unconscious less than twenty-four hours was only 7½ per cent and that for the cases of prolonged unconsciousness 17 per cent, while for the patients unconscious twenty-four to forty-eight hours it was 70 per cent and for those unconscious forty-eight to

seventy-two hours it was 67 per cent. This further emphasizes the point previously made that the second and third days constitute the critical period for unconscious patients.

*Prognosis for Complete Recovery.* A surprisingly large proportion of the patients in whom unconsciousness was prolonged for days or weeks recovered without residua. Of the twenty-five who lived eighteen or 72 per cent made such a recovery; this amounts to 60 per cent of the whole group of thirty patients. The percentage was about the same (74 and 75) for the non-operable and operable groups (Table VI), but there were no mental disturbances among the operable cases as compared with four in the non-operable group. One patient presenting complications also had mental residua. It is to be anticipated that some of these five may yet recover, for Martin (1937) has shown that "even when mental symptoms are prolonged their course is towards recovery and in the majority of cases recovery is eventually complete." He goes on to state that most of the patients in whom it does not become complete are over fifty-five. In this view Russell (1932) concurs, saying that "patients above 40 or 50 are much less likely to recover fully." Two of the five cases mentioned are over fifty and one of them has been committed to a mental hospital.

Glaser and Shafer (1932) reported residual neurological signs in 32½ per cent of cases of skull and brain trauma, and an incidence of mental changes of 9 per cent. These figures are practically the reverse of the 20 per cent mental residua and 8 per cent neurological residua found in the cases of prolonged unconsciousness reported herein. The comparison suggests, at least, that in cases of craniocerebral injuries in which loss of consciousness persists for longer than seventy-two hours the proportion of patients who have residual mental changes will be greater, and the proportion of neurological changes less than in ordinary head injury. The observation again contradicts the opinion of Russell (1932) that the duration of unconsciousness bears little relation to prognosis.

*Treatment.* It is obviously impossible to draw any conclusions with regard to the efficacy of treatment by any given means in a series of thirty cases. Certain broad principles have seemed to make themselves evident in the study of these patients and in the observation and treatment of a number of them, however, which appear to be worth enumerating. In the last analysis they differ little from those principles which most authorities accept as basic in dealing with any head injury.

First of all, as little as possible should be done to the patient. *X*-rays should be postponed unless there is a question of a depressed fracture. Restlessness may be controlled by sedation but opiates should not be given. An adequate examination is essential but the patient should be disturbed as little as possible. This first principle is in a sense an argument against lumbar punctures, particularly in view of Jefferson's (1932) opinion that compression is not an important factor in unconsciousness and his observation that at operation one is likely to find a low pressure brain with a contused temporal lobe. Furthermore, Zierold (1935) who measured the spinal fluid pressure in 128 cases of severe head injury by lumbar puncture found that "abnormal intracranial pressure is not a frequent occurrence." In 83.6 per cent of his cases the cerebrospinal fluid pressure was less than 180 mm. of water and only in 5.4 per cent did it exceed 300. Bagley, however, emphasizes the value of removing bloody cerebrospinal fluid in cases with associated subarachnoid bleeding (1941).

Secondly, a careful and frequent check of temperature, pulse and respirations, blood pressure and responses should be made and charted. This is extremely important in determining the operability or non-operability of the case. Cerebral decompensation may occur very quickly, and it may be necessary to recognize it at once,

if the patient is to be taken to the operating room in time to save his life.

In the third place, careful attention should be paid to the fluid balance. The urine output is the best guide here. Bladder disturbances are dealt with by instituting drainage, both for the purpose of providing information concerning the output and for the protection of the bladder itself. It seems doubtful whether dehydration methods are of value in cases of prolonged unconsciousness, because of their disturbing effects on the body water in general when used over a period of days and because compression is not usually a factor, as has been mentioned above.

A fourth consideration is supportive treatment and this is of vital importance. Debilitation and infection are two great dangers. Transfusions may be given early for shock, and later to provide protein, and to aid in combatting infection. Tetanus and gas bacillus antitoxins, and chemotherapy should be administered as indicated. Parenteral vitamins should be given from the start and feeding by gavage begun as soon as feasible. Nursing care with special regard to frequent changes in position and attention to the respiratory passages, mouth and skin are of great importance.

These cases differ markedly both as to the underlying pathological condition and as to treatment from those in which the patient regains consciousness and then loses it again, whether rapidly or slowly. The former instance has long been considered pathognomonic of extradural hemorrhage and immediate operation is imperative. The latter suggests a subdural hematoma or hygroma and steps to establish the diagnosis and remove the clot or fluid should be the focus of emphasis. Other complications tending to produce secondary stupor are subarachnoid hemorrhage, brain abscess, intracranial pneumatocele, and rarely depressed fracture and post-traumatic psychosis.

It should be emphasized that any of the above enumerated complications of cranio-cerebral injury may occur when the state of unconsciousness is due to the magnitude of the brain damage alone and important signs including secondary stupor masked thereby. This again calls attention to the importance of keeping a detailed record of the patient's pulse, respirations, temperature and responses and of making frequent neurological examinations throughout the period of recovery, so that indications for exploration shall not go unnoticed.

## CASE REPORTS

Certain details in the treatment of patients showing prolonged unconsciousness may be illustrated by the following case records:

Case 1. G. S., a white male, aged twenty-four (U.M.H. No. 95815) was brought into the Union Memorial Hospital accident room November 15, 1941, in an unconscious state following an automobile accident. He was said to have called out the name of his companion immediately after the crash and lapsed into unconsciousness. His past and family history was noncontributory, except that it is interesting to note that his father was unconscious seventeen weeks following a head injury and incapacitated two years, but eventually recovered completely.

Examination revealed the temperature to be 98.4°R., pulse 80, respirations 20, blood pressure 118/60. He was a well developed and well nourished white male, deeply unconscious, moving his left side little but thrashed around with the right extremities. The pupils were only pinpoint in size and reacted very little to light; the eyes were roving. The fundi were negative except for left corneal opacity. There was a large bruise about the left eye. There was no bleeding from ears, nose or mouth. Neurological examination showed only some flaccidity of the left side as compared with the right and an equivocal Babinski response on the left. The thorax and abdomen were negative. He was admitted to the hospital for observation.

The pulse stabilized around 90, the temperature around 101° rectally, and the respirations at eighteen to twenty for three days. The state of consciousness continued to be deep coma. The patient received 1,500 cc. of intravenous

fluids daily. Seventy-four hours after the accident the temperature, pulse and respiration fell rapidly within an hour to 99, 60, and 12, respectively, with periods of apnea. By this time some spasticity of the left side had developed. The patient was taken to the operating room at once and a trephination of the right temporal region done. About 50 cc. of straw-colored fluid under high tension spurted out as soon as the dura was opened; after this about 15 cc. of old blood which had apparently been enclosed in a separate membrane higher over the cortex was evacuated. No cortical damage was seen and the brain pulsated normally after this procedure. A subtemporal decompression was done, two gutta percha drains inserted and the wound closed.

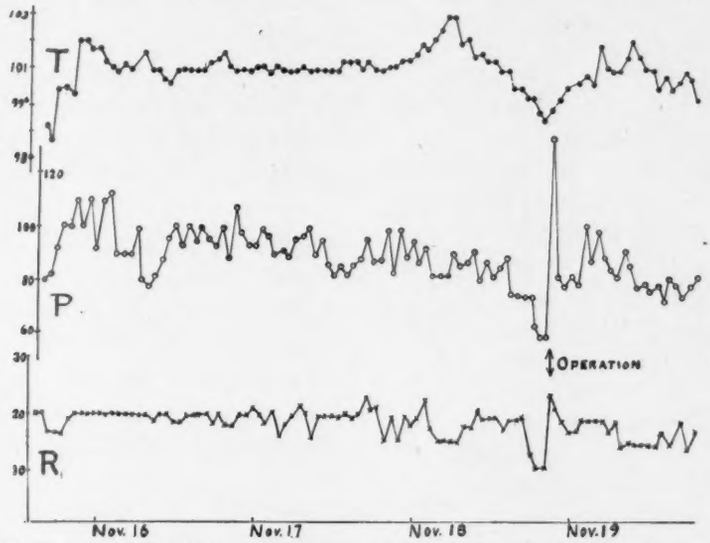


Fig. 1. A chart of the temperature, pulse and respirations in Case 1 during the first five days. The break in compensation near the end of the fourth day and the restoration of compensation following operation is clearly shown.

The pulse which had spiked to 160 during the operation but returned to 84 at the end came down gradually over the next thirty-six hours and stabilized in the sixties. The temperature was normal forty-eight hours postoperatively and remained so. The respirations were frequently very slow, sometimes 10 or 12. The cranial wound drained cerebrospinal fluid profusely for six days. Thereafter the decompression wound remained soft and consequently no further operative procedure was done. The patient received intravenous fluids and parenteral vitamins. A transfusion was given on the sixth postoperative day.

Twelve days after his accident the patient swallowed small amounts of fluid administered by syringe, and on the eighteenth day recovered consciousness as defined in this paper, recognized his wife and called her by name. Three days thereafter he was able to receive an adequate fluid intake by mouth. The left side continued to be paralyzed and it was believed that this must be due to intracerebral damage. Recovery was slow but progressive. There was some mental confusion until shortly before discharge five weeks later. On discharge there was still some memory deficit with a tendency to confabulation and a left hemiplegia.

The patient was followed in the out-patient department. Six months after the accident he was able to walk well and the usual tests of judgment, memory and general information were well performed. The left arm remained paralyzed, but there was good movement from the shoulder and the patient made use of it. No epileptic episodes had occurred.

*Comment.* This case is of particular interest in reference to the recent report of Scott (1942) concerning prolonged stupor produced by subdural hygroma. Since this patient did not recover consciousness following the evacuation of his hygroma, it was evident that some deeper pathological process was at work and this was further

indicated by the persisting paralysis. The process is believed to be intracerebral in nature. One of Scott's patients (11) was out on supra-orbital pressure. Abrasions and hematoma of the left side of the head were present. Both pupils were small, the right

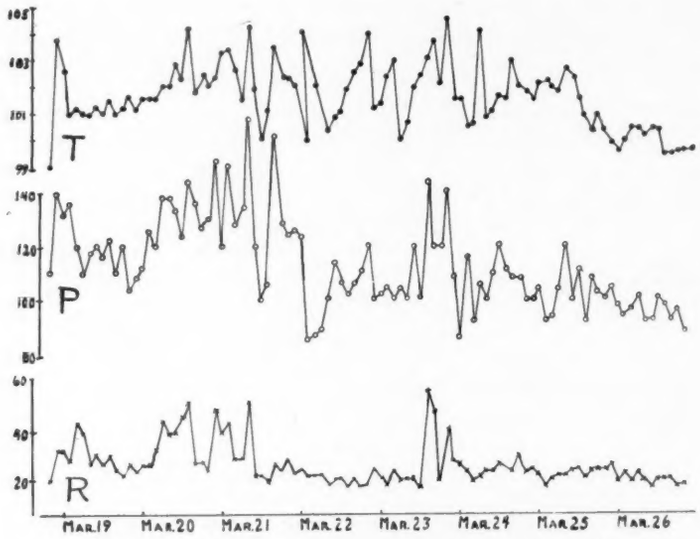


FIG. 2. A chart of the temperature, pulse and respiration in Case III during the nine days following injury. The precarious state of the child is obvious from the wide fluctuations, and the final establishment of cerebral compensation on conservative treatment alone is evident.

unconscious a total of twenty-nine days and accordingly falls into the group of cases with which this study is concerned. The other two regained consciousness following head injuries to become stuporous again later and fall into what must be considered definitely an operable group.

A chart of the temperature, pulse and respirations in Case I is shown in Figure 1. The first five days are shown and the chart illustrates the suddenness of onset of cerebral decompensation and emphasizes the importance of careful and frequent recording of the vital signs.

CASE II. M. J. G., a white male of five years, (U.M.H. No. 83301) was brought to the Union Memorial Hospital accident room September 7, 1940, shortly after he had been struck by an automobile. He had been picked up unconscious and arrived at the hospital in this condition.

Examination showed a temperature of 100.4°R., pulse 90, respirations 26, blood pressure 132/80. He was a well developed and well nourished child in coma. He moved and cried more so than the left, but they reacted well to light. There was no bleeding from the ears, nose or throat. The neck was slightly stiff but the thorax and abdomen were negative. The neurological examination showed some flaccidity on the left side, but the reflexes were everywhere equal and active, except for absence of the abdominal reflexes. There was bilateral unsustained ankle clonus and no Babinski. There were no other positive findings.

For the first twenty-four hours the pulse was 130 to 140 and the temperature 101 to 102° rectally. The child was deeply comatose most of the time, but occasionally would cry out irrationally when disturbed. By the third day the pulse and temperature were nearly down to normal and the child opened his eyes but did not respond. The patient's general condition improved over the next three days, and by the sixth day had begun to move the left side a little, the leg more than the arm. On that day the patient spoke a few times. "I want some milk." "Give me a cracker." Thereafter the child appeared alert, but was very irritable and unstable. By the end of another week he was using the left side better and was able to stand. On discharge on the sixteenth day after

injury his mental state was clear and there was minimal difficulty in the use of the left arm and leg.

*Comment.* This is a case in which some neurological residua were present despite a relatively short prolongation of unconsciousness. It may be contrasted with Case III in which the period of unconsciousness was four times as long with minimal residua.

It is this type of case that makes it necessary to be particularly guarded with regard to prognosis. Prolongation of unconsciousness is, of course, in itself an indication of severe disruption of cerebral function, and while the study reported here shows that the outcome is often much better than one would hope, a fair percentage of the patients still have residua.

Case III. R. H., a white male, aged three years, (U.M.H. No. 98443) was brought to the accident room of the Union Memorial Hospital on March 18, 1942. He was said to have run into a moving car fifteen minutes earlier and to have been unconscious when picked up. No convulsions or bleeding about the head had been observed.

Examination revealed the temperature to be 98.8°R., pulse 108, respirations 20, blood pressure 90/60. He was a well developed and well nourished child deeply unconscious. Respirations were deep and somewhat irregular and his color was good. There were several abrasions of the legs but no lacerations or hematoma about the head and no gross skull injury. The eyes moved aimlessly; the pupils both reacted well to light; the right pupil was slightly smaller than the left. Fundi were negative. There was no bleeding from the ears, nose or mouth and the thorax and abdomen were negative. Neurological examination showed all extremities to be slightly spastic with hyperactive reflexes and positive Babinski and Oppenheim signs bilaterally. Bilateral ankle clonus was also noted, but no Hoffman. Abdominal and cremasteric reflexes were absent. A slight writhing of the body was observed on supra-orbital pressure. The patient was incontinent of urine.

The child was admitted to the hospital three-quarters of an hour after the accident. On admission the temperature was 99° rectally and the pulse 110. Ten hours later both had gone sharply upward—to 103.8° and 140, respectively. During the next twenty-four hours the child was more restless and seemed to move the right side slightly better than the left. There was no change in the state of consciousness or the reflex picture. The pupils were now equal.

During the next five days the boy's temperature spiked to 103° or over twelve times. Each time it fell about two degrees after sponging. The pulse and respirations followed the temperature, the former ranging from 84 to 170 and the latter from 20 to 48. (Fig. 2.) Thereafter the temperature remained slightly elevated most of the time, but did not go over 102° rectally. The pulse stabilized at 80 to 120 and the respirations at 20 to 24. The temperature was normal after twenty-seven hospital days and the pulse 90 to 100.

The child was given intravenous fluids until the thirteenth day when feeding by gavage was begun. Parenteral vitamins were given until administration by mouth was possible. *X*-rays on the fifteenth day showed no fracture and a diagnostic lumbar puncture on the seventeenth day revealed clear, colorless fluid under a pressure of 90 mm. of water—Pandy negative, no cells.

On the sixteenth day the patient would follow objects with his eyes and grasp the observer's finger with the right hand, although he moved the left side little. On the twenty-sixth day he was able to take liquids by mouth and was moving the left side as much as the right. By the thirty-fourth day he could pull himself into a sitting position, speak, recognize persons, drink out of a glass and eat with a spoon. Two days later he was walking with a somewhat spastic gait. Five days later he called a visitor by name and asked for the urinal.

The child was given physiotherapy and had a good return of muscular function. He was discharged well after sixty-five days in the hospital. On discharge there was a minimal weakness detectable on examination on the left side, but this was not noticeable in the boy's activity. The reflexes were active; none were abnormal and there was no clonus. The cremasteric and abdominal reflexes were present. The mental state was clear and the intelligence appeared normal for a child of three.

*Comment.* This case is remarkable for the obviously terribly severe nature of the cerebral injury as compared with the completeness of recovery. It may readily be contrasted with Case II in this respect. The result in this case is attributed to the fact that therapy was ultraconservative and that no added insult was superimposed on the original brain damage. In the first desperate days when the patient swung many times out of the range of cerebral compensation, the temptation to perform operative exploration was strong, but it seems reasonable to suppose that any such attempt would have resulted in the depletion of the child's feeble reserves and death.

The question may be raised whether bilateral taps might not have hastened recovery. In answer to this it can only be said that at no time did there seem to be a definite indication for operation when the child seemed at all likely to survive the simplest procedure. In fact, as late as the fifteenth day when skull *x*-rays were taken—and this was done with considerable circumspection—the condition of the patient was affected very adversely and it was feared for a period of hours that he was going to die.

It was just as important to recognize the non-operability of this case as the operability in Case I. These histories serve to emphasize the fact that there is no substitute for careful, continual observation of the unconscious neurosurgical patient.

Case IV. L. B., a white male, aged sixty-two years, (U.M.H. 87083) and a fire chief by profession, was brought to the Union Memorial Hospital accident room in an unconscious state. He had suffered a head injury in an automobile accident. He was bleeding about the head when picked up and draining clear fluid from both ears.

His temperature was 97.4°R., pulse 90, respirations 26, blood pressure 160/90. The patient was a well preserved male of sixty-two years. There were lacerations of the forehead and drainage from both ears which was obviously cerebrospinal fluid. There was no blood or fluid from nose or mouth, no evidence of depressed fracture. The pupils were equal and reacted to light, but the eyes moved aimlessly. Fundi were negative. The heart was not remarkable. Both lung fields were resonant, but many coarse râles and rhonchi were heard. There was mucus in the throat; the abdomen was negative but there were no positive findings on neurological examination.

The patient's course was satisfactory for ten days although he remained unconscious. At times there was respiratory embarrassment when the respiratory rate would be as high as 40. The temperature ranged between 101 and 102°. A lumbar puncture on the ninth day showed xanthochromic fluid under a pressure of 205 mm. of water. The patient did not rouse from coma, although he was restless at times.

On the eleventh day a massive collapse of the left lung occurred. Bronchoscopy was performed and a mucous plug removed. The next day, however, a second massive collapse of the same lung occurred. Treatment was unavailing this time and the patient died twelve minutes after the collapse occurred.

*Comment.* This case is presented as an example of a "complicated" craniocerebral injury in which unconsciousness was prolonged and in which death occurred. The death, however, is obviously to be attributed to the complication rather than the actual injury to the head, although the severe nature of that injury was evident from the presence of cerebrospinal otorrhea. The importance of skilled nursing care in cases such as this cannot be overemphasized. Careful attention to frequent changes in position and keeping the respiratory passages clear by means of suction is imperative.

The four case histories given in detail have served to illustrate the types of problems which arise when a craniocerebral injury is followed by prolonged unconsciousness and to emphasize certain points in regard to the care of these patients. The outcome in three out of four of these patients and in the great proportion of these thirty cases of head injury in which unconsciousness was prolonged shows that unsparing effort in the care of such patients is well worth while.

## SUMMARY AND CONCLUSIONS

1. Two hundred twenty-four cases of craniocerebral injury have been studied and among these there were thirty cases in which unconsciousness was prolonged. The mortality was 12 per cent for the whole group and 17 per cent for the cases in which unconsciousness persisted for more than three days.

2. When an unconscious patient has survived the first critical seventy-two hours following craniocerebral injury, the prognosis both for survival and for recovery with little or no residua is good—83 per cent for survival according to this series with 72 per cent of those living making a complete recovery.

3. Treatment in these cases should be conservative, providing adequate fluid and nutritional supply. Care should be taken to ward off infection either intracranial or general. Operative intervention should not be undertaken on the basis of prolonged unconsciousness alone.

4. Persisting unconsciousness may mask the presence of such complications as extradural or subdural hemorrhage, brain abscess, etc. A careful record of the temperature, pulse, respirations and blood pressure plus frequent neurological examinations will reveal the presence of these in adequate time for the institution of operative treatment.

5. Cases in which consciousness is regained and is lost again do not belong in this group; such patients are candidates for immediate surgical exploration.

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# PATHOGENESIS AND EXPERIMENTAL THERAPY OF KELOIDS AND SIMILAR NEOPLASMS IN RELATION TO TISSUE FLUID DISTURBANCES

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IT is the purpose of this communication to review the known facts on the pathogenesis of keloids, and related clinical entities, in view of recent observations which have been collected by the authors.

The presence of such new growths is most discouraging to both the patient and surgeon, for the disfigurement which such a process produces is a matter which imposes delicate judgment in respect to therapy. Christopher[1] has written that "Scars are produced in the process of healing of tissue injuries and result in deformities which may be unsightly if visible. When disfiguring, they may cause mental distress and influence the activities of the bearer . . . Should there be a combination of trauma and disease, the resultant deformity will be greater."

Marshall[2] has summarized the psychological upsets which have been produced by the disfigurement of acne, and these findings are similar in nature to those which are found in patients with visible keloid growths. The keloid is indeed more vicious, for the sufferer may be well aware of the therapeutic shortcomings of the many measures now employed in this disfiguring lesion.

## ORIGIN OF PRESENT STUDY

Marshall[3] has recorded some observations with the use of a special material made from liver extract which has improved cases of acne vulgaris. In this study, he observed that various scars produced by acne seemed to disappear partially through a partial absorption phenomenon. He was able to demonstrate this action on the basis of a vasoconstricting substance which he believed was present in his experimental fractions which were prepared from liver extract. The unusual physiological action of his preparations led him to the belief that scars and other allied processes may be at least semireversible. In other words, in skin areas which exhibited a venestasis, the vasoconstricting principle improved these areas by partially checking the outflow of fluid from the dilated blood vessels. He observed, further, that as these areas became whiter in color because of the vasoconstricting action of this material, which was injected subcutaneously about twice a week, the size of the hypertrophic scars was lessened to a marked degree.

In order to apply these findings on vasoconstriction to wound-healing, he found that wounds improved in healing by vasoconstriction which was produced by the application of ice compresses to the surgical site. Among the applications of other principles, which are of importance in wound-healing, was the matter of asepsis and the use of adequate doses of vitamin C,[4] which seemed to assist in the formation of a scar of strong tensile strength and the adequate healing of the tissue injury without hypertrophic changes.

While this observer was engaged in this research, he had the occasion to study the effects of his experimental vasoconstricting material on patients with keloids and hypertrophic scars.

Since these observations appear to be of importance in our present concepts of the pathogenesis of keloid formation, it is our wish to review the basic mechanisms which seem to be intimately connected with such a process.

Yates and Raine[5] have published an excellent review of the functions and the diseases of the lymphatic system.

## NATURE OF KELOIDS AND RELATED ENTITIES

A keloid is a non-inflammatory fibroma.[6] The keloid differs from the hypertrophic scar since it involves skin areas beyond the limits of injury.[7] Hypertrophic scars contain small collagen fibrils while keloids are composed of large collagen fibrils.[8]

Hypertrophic scars, keloids, the nodulus cutaneum of Arning and Lewandowsky, and induratio penis plastica, are included under the group of hard fibromas, according to McCarthy.[9]

The nodular subepidermal fibrosis of Michelson, or the fibroma simplex, according to Becker and Obermayer,[10] consists of slightly elevated and firm nodules which may be noted on the thighs or legs, trunk, or even the arms. They may appear singly, but they may be multiple and are not grouped. Their color is, at first, rather erythematous, brownish later on, after which they appear elevated or depressed due to regression. They retain their firm nodular character. Becker and Obermayer have described these neoplasms as subacute or chronic inflammations which are accompanied or are followed by fibrosis. They have written that the tissue is highly cellular at first, but this tends to become more fibrotic later on. The infiltrate blends imperceptibly into the adjacent normal connective tissue and the lesion is not encapsulated as is the fibroma durum.

According to Christopher,[11] scars are composed mostly of connective tissue with a thin epithelial covering. Sweat and sebaceous glands are absent usually, and this loss apparently affects the normal skin lubrication. The connective tissue fibers in scar tissue are more dense and less elastic than are the connective tissue fibers of normal skin.

Christopher has written that the factors which produce hypertrophic scars are not fully understood, for some individuals have a tendency to develop them while others do not. Keloids, when excised, almost always have the tendency to recur.

Similarly, the cause or causes of keloid formation are not definitely known. Becker and Obermayer believe that a definite predisposition to their formation must be assumed. There is evidence which points to a familial tendency in this disorder. A recent communication by Garb and Stone[12] postulates a hormonal disturbance, the nature of which is unknown.

From the microscopic aspects, keloids are composed of quite cellular fibrous tissue, and these fibers cross in several directions, parallel to the surface. Becker and Obermayer have made a definite point by stating that, as the keloid progresses, the cellular elements diminish and the neoplasm is composed chiefly of collagen bundles. Rarely does spontaneous regression take place and the possibility of malignant degeneration must be kept in mind.

In other words, when a wound heals normally there is a cessation of fibrous tissue formation as soon as continuity is re-established. However, this is not the case in keloid formation, for here the proliferation of fibroblasts continues with "piling up," as it were, of fibroblasts. This results in the formation of the new growth which is called a keloid, and which is a firm, fibrous, non-elastic connective tissue proliferation. Bundles of coarse, large connective fibers intertwine in all directions.

Becker and Obermayer[13] have described the keloid as "at first erythematous, smooth, with an appearance of tenseness of the superficial epithelium and telangiectasis over the surface." Keloids often project peripherally in the form of one of several "feet" which extend into normal tissue. The character of the keloid depends somewhat on the extent of initial injury. These lesions usually grow to a certain size and then remain stationary. As the keloid grows older, it becomes very firm, less erythematous, and eventually may be flesh-colored or paler than the surrounding

skin. The so-called "spontaneous keloids," i.e., lesions which arise without demonstrable previous injury, are usually located in the sternal area of the chest. It may be assumed that microscopic injury gave rise to their growth just as keloid formation follows follicular pyogenic infection in predisposed individuals (acne keloid). Keloid is much more frequent in the Negro. It often occurs following burns, either chemical or caloric. Strangely enough, not all injuries in a susceptible individual are followed by keloid formation. Huge keloids have developed after piercing ear lobes for ear rings, while accidental cuts or other injuries in the same person have resulted in ordinary scars. This is probably the result of variation in the local response in the same individual.

McCarthy[14] has described three types of keloids: The first type is "the spontaneous or true keloid" which arises without any trace of injury or infection and occurs symmetrically on the chest in the form of whitish plaques or flat nodules, which by the formation of peripheral fibrous strands, seem to merge gradually into the surrounding skin. The second type is "the false or scar keloid" which results from injury as does the hypertrophic keloid, the third type, which it resembles. The scar keloid proliferates and extends laterally beyond the limits of the original lesion, while the hypertrophic keloid grows in an upward direction, producing, as the name indicates, a tumor that projects above the normal skin level. Histologically, the papillae may be involved secondarily, but the keloid always begins in the cutis or subcutis and never in the papillae. As it grows upward, the papillae are involved and, therefore, there is no histologic basis for separating the true from the false keloid. Young keloids are different in appearance than older ones.

In young keloids, unless recently injured, the epidermis and the papillae are normal. If the keloid is deep in the skin, the cuticular appendages are untouched. The tumor mass is made up of young connective tissue extraordinarily rich in cellular elements. The connective tissue bundles are not easy to make out. The cellular elements have a tendency to group themselves in certain regions in the form of ill-formed whorls which Warren, Unna and Joseph thought resembled vascular periadventitia and were probably the points of origin of the keloid. The cells have long oval bodies with large vesicular nuclei which show numerous regular mitotic figures.

As the keloid ages, the collagenous fibers appear and connective tissue bundle formation takes place at the expense of the cellular elements which are gradually compressed and progressively diminish in number.

With Weigert's lithium-carmine stain, we see that the tumor is made up of coarse, intertwining tissue fibers which are poor in cellular elements and sharply limited from the surrounding normal tissue. The tumor mass is, as a rule, entirely free from elastic fibers, and it offers a sharp contrast to the surrounding skin with its normal elastic fiber content. In others, a few fine shredded fibers can be made out. Above the tumor and separating it from a normal epithelium is a narrow zone of normal supporting tissue.

In the end stage this hard fibrosed tumor mass appears to be enclosed in a capsule not of its own making but rather due to the compression of the immediately surrounding normal connective tissue (pseudocapsule). Mucoid degeneration (pale red with polychrome methylene blue stain) can be made out in some of the fibers of this pseudocapsule. As a spontaneous keloid continues to grow, it extends in all directions and eventually destroys the papillae and presses upon the overlying epithelium which shows signs of a general thinning and an atrophy of the individual cells. At this stage the true keloid presents no histological differences from the false keloids. It is evident that as the false or scar keloids arise secondary to the previous disturbance (trauma or infection), the papillae have already been destroyed and

the keloid may arise in any layer of the skin, depending upon the depth of the previous injury or infection.

## PHYSIOLOGICAL PRINCIPLES WHICH ARE INVOLVED

In order to understand what factors govern the normal flow of the tissue fluids, and what possibly may happen to this delicate mechanism when such neoplasms as keloids and hypertrophic scars develop, a review of the basic physiological principles will be undertaken at this time.

*The Nature of Tissue Fluid.* According to Best and Taylor,[15] water makes up approximately 70 per cent of the body's weight and extracellular fluids account for about 20 per cent, while the skin contains about one-fifth of the total water in the body. These investigators have stated that this body water is practically all in the free state, since substances can be dissolved in it and they can also be removed from the body water by ultrafiltration. Colloids and other chemical constituents actually bind very little water. The concentration of potassium in the interstitial fluids and the blood is only a small fraction of the sodium concentration, while in the tissue fluids, the concentration of sodium is much less than that of potassium.

The body tissue fluid including the intracellular skin fluid, is composed of serum globulin, fibrinogen, and serum albumin, while elastin and collagen, which enter into the formation of protective and connective tissues, are classified as albuminoids. Collagen enters into the formation of actual connective tissue, while elastin is used in the synthesis of elastic tissue.

*The Mechanisms of Tissue Fluid Exchange.* There are two factors which influence this interchange between blood vessels and the tissues: (1) Osmotic pressure: This is the drawing force which certain solutions have on the body solution (tissue fluid) when separated by a semipermeable membrane. This osmotic pressure is, in turn, governed by certain physical laws. (2) Hydrostatic pressure: This is the actual pressure within the capillaries which has been produced by the force of the heart's pumping action, the blood pressure, and its relation to that of the extravascular tissue fluids.

As has been mentioned, the following plasma proteins are in solution: albumin, globulin, and fibrinogen. Since albumin has the smallest molecule, it escapes more freely than do the others.

Best and Taylor[16] have recorded that "the osmotic pressure of the plasma, if anything, increases as the blood passes along the capillary as a result of the passage of water outwards, and the consequent rise in the concentration of the protein. That is, the force holding fluid within the vessel is increased. The hydrostatic pressure, on the other hand, falls gradually from the arterial to the venous end of the capillary. Near the arterial end the blood pressure is greater than the osmotic pressure and a filtration of fluid of low protein content will result. Near the venous end the hydrostatic pressure may fall below the osmotic pressure and a flow of dilute fluid (water and salts) from the tissue spaces into the blood will be brought about. Transudation of a dilute plasma and re-absorption of a saline fluid, respectively, are continually going on in these two regions of the capillary bed. Metabolic processes in the tissues bring about changes whereby larger molecules are being broken down into smaller ones; other molecules are removed or built up into larger ones. In this way, alterations in molecular concentrations and in the diffusibility of the constituents of the tissue fluids with consequent variations in osmotic relationships are occurring ceaselessly. Under any circumstances in which the blood volume is increased or diminished, either the hydrostatic pressure or the osmotic pressure or both are altered, and it is through such changes that the blood fluid is restored automatically to its previous level."

*Lymph Formation and Circulation.* The forces which control the regulation of the

tissue fluids are concerned directly in the formation of lymph, since these two processes are interrelated and quite similar, with the exception that the protein portion of the fluid passes into the lymph channels where it is returned to the body economy through the blood stream. The lymph also has the ability to absorb other colloids.

Capillary filtration is directly proportional to the increase in venous pressure, for extracapillary pressure is followed by a fall in the filtration rate, because of the fluid accumulation which opposes the hydrostatic pressure in the capillary system.

Increase in the permeability of the capillary wall is produced by: (1) Rise in temperature, which increases the lymph flow and the filtration rate; (2) reduced oxygen supply (anoxia) through damage to the capillary endothelium. An increase in the flow of lymph is produced by: (1) The formation of metabolites which increase the osmotic pressure of tissue fluids and thus pull in more fluids from the tissues; (2) vasodilatation and the increased capillary pressure. Similarly then, a decrease in the metabolites in tissue fluids, or vasoconstriction, with a decrease in capillary pressure, will retard the flow of lymph or tissue fluids.

Some of the major causes for the production of tissue edema can be effected through the reduction of the osmotic pressure of plasma, the general or localized changes which can be produced in capillary blood pressure, the increased permeability of the capillary membrane, obstruction of the lymph drainage channels, the mechanical obstruction of veins, or from edema due to cardiac decompensation, from renal disease itself, or from the ravages of tissue infection.

*The Unusual Anatomy of the Skin Vessels.* Becker and Obermayer[17] have adequately summarized this feature in stating that "small arteries supply the superficial portion of the body. The course of the artery is through a cone-shaped area with its base at the surface and its apex in the subcutaneous tissue. The vessel divides time and again, unites itself in at least two anastomotic plexuses and terminates in capillaries in the papillae. From there, the blood enters small veins which unite with other venous tributaries to produce another cone-shaped system. The junctions of the bases of these cones form the network seen in cutis marmorata and certain other vascular conditions. The same artery supplies blood via capillaries to the tissues making up the dermis, and to the glands contained therein. The venous drainage is similar. The lymphatic drainage of the skin is through tissue spaces originating between the cells of the prickle-cell layer, thence into the dermis, in the middle portion of which are the first lymph channels. These anastomose and unite with other channels and to course with the blood vessels and nerves through the subdermis as tributaries to the larger lymphatics in the deeper tissues."

## LOCAL EFFECT OF EXCESSIVE LYMPH OR TISSUE FLUIDS IN VARIOUS[1] DISEASES

Ordinarily, lymph stasis produces edema and the tissue spaces are engorged by any one or more of the causes which have been described heretofore. Because of its low fibrinogen content, lymph, or tissue fluid, will not tend to coagulation.

However, the influx of lymph or tissue fluid, which produces an enlargement of the lymph spaces, will stimulate the production of fibrous (connective tissue) tissue in the involved area.[18]

Perhaps a short summary of such a phenomenon, in the course of several diseases, may demonstrate the tendency of the stimulus, for the formation of fibrous tissue, when a lymphatic transudate of fluid is present.

In cases of filariasis, the venous return and the lymph exits are blocked by the Filaria bancrofti, and early cases exhibit a large amount of coagulable fluid from the lymph spaces and the connective tissue. This gives the impression, on examining such tissues microscopically, that the tissues are injected with gelatin.

As the disease progresses, definite fibrous connective tissue is formed in the dilated lymph spaces and channels. Progressive local hypertrophy is a clinical characteristic of this disease. Even the skin in these cases shows an edema with a resultant hyperplasia of the connective tissue of the skin itself, as well as the subcutaneous tissues.

This extravasation of tissue fluid is noted also in other portions of the body in various diseases. This transudate is usually straw-colored or it may be colorless. Of particular interest is the fact that fibrinogen is present along with the serum albumin and the globulin fractions. Peculiarly enough, the presence of fibrin is rather rare. The endothelial cells of the lymph spaces may be present along with some red and white blood cells. However, this transudate contains most of the known materials which can respond to cellular injury and may thus initiate the formation of connective tissue.

As is the case with the cellular spaces in the skin, such a transudate may push the tissue cells apart, and if this process continues, fibroblastic growth may be initiated. Since identical processes can occur in other parts of the body, such transuded fluid in the interstices of the tissues is termed an *edema*. If it happens to occur in serous cavities, the extravasation is called *dropsy*. Its presence in the pleural cavity is termed *hydrothorax*, and in the heart lining (pericardium) *it is hydropericardium*. Other similar transudates are the hydrocele, hydroperitoneum, etc. Hence, the thickening or hypertrophy of such structures is usually preceded by the presence of a serous extravasation with subsequent formation of fibroblastic (connective) tissue.

Therefore, such disorders as anasarca, trichiniasis, syphilitic tarsitis, myxedema (especially the thickening of the eyelids), Mikulicz's disease, Milroy's disease, chronic lymphatic obstruction, acromegaly, myositis, anthrax, pleurisy with effusion, fibrinous pericarditis, also certain forms of arthritis, all have shown, at one time or other, the presence of a serous transudate which was produced by various pathological processes. In many cases, the excessive lymph, or tissue fluids, had been followed by the formation of connective tissue as a defensive or compensatory measure. This effect is, perhaps, more intensified when infection, or the addition of foreign bodies, are added to the effect of excessive lymph or tissue fluid.

## PATHOGENESIS OF KELOIDS AND RELATED ENTITIES

Geschickter and Lewis[19] have written about hereditary and congenital predisposition as definite factors in keloid growth. Calcium metabolism and a localized endocrine disturbance were thought responsible.

Nason[20] states that trauma is always the etiologic precipitating factor in the production of keloids. There is a certain "fibroblastic diathesis" which varies in intensity among races and individuals.

Filips[21] believes that the underlying cause of keloid formation is the hypersensitivity of the fibroblast and the vascular endothelial cells to any agent having the power to mobilize those elements in the protein of these cells which induce them to proliferate.

Drinker and Field[22] have produced experimental edema in dogs by injecting the lymphatics with silica. They quote Manson who did not believe uncomplicated lymphatic obstruction could cause elephantiasis, since infection must be present also. This lymph blockage shows that the fibroblasts are the first cells to grow. This is true in tissue cultures and these authors believe that it is also true in the body when a medium is present which is rich in blood protein and the products of cell destruction. Venous obstruction produces the same situation and the tissue fluid, under such circumstances, is not far different from that of inflammation and, hence, the environment for fibrous overgrowth is simply provided in a more ideal form than can be

the case with uncomplicated block of the lymphatics.

Bearing these observations in mind, we can return to the matter of keloid formation. In the skin there are multiple strata which are composed of various types of skin cells, and the tissue spaces are readily accessible to any extravasation of excess tissue fluids which might be produced by an increase in capillary pressure. The dilatation of the blood supply occurs with a slowing of the blood stream in such a case. Hence, lymphatic drainage may be obstructed, so that the transudate of lymph material escapes from the vessels. The edema is rather localized to an area of varying size which involves the site where lymph is present in excessive quantity.

Since it has been shown that early keloids and hypertrophic scars show the presence of a collagenous material, microscopically, it may be assumed that this collagen is closely related to the edematous material which precedes the formation of connective tissue. The connective tissue proliferation develops as the keloid grows older, and the serous material is never completely absorbed, but connective tissue continues to develop until a partial quiescence occurs.

The clinical appearance of the keloid coincides with scopic changes, for the keloid is soft to the touch in its early stage, but becomes firmer to the touch as connective tissue is developed.

Thus, it is the localized edema, followed by the laying down of connective tissue, which causes pressure to be exerted in the tissue spaces. This pressure is directed upward, since the force of least resistance is at the surface. Atrophy of the epithelial skin covering takes place and this results in the so-called pseudocapsule to which the pathologists have referred.

As this process develops, with the involvement of adjacent areas of the skin, the size of the neoplasm increases and its growth and extension of contiguous skin tissue ceases only when the surrounding tissues can compensate for the disturbed flow and stops in the tissue fluids present in the keloid.

The "trigger" mechanism in keloid formation appears to be similar, therefore, to the phenomenon of diapedesis which causes some individuals to bruise so easily or to develop idiopathic purpuric spots. In the case of keloid growth, it is the extravasation of lymph, while in the other, it is the loss of blood through the vessel walls because of their lowered permeability.

It is known that much serum escapes from third degree burns. That is why multiple plasma transfusions have been indicated for the shock which such a condition produces. This is due, in part, to the escape of fluid from the vessels into the tissue space.

Furthermore, third degree burns are known to produce keloid formation readily. It is logical to assume that this formation of excess fibrous growth may be due, in part, to the great amount of serous exudation which seeps from the wound area. If this transudate remains stagnant in the burned tissues for some time, an excessive amount of connective tissue is liable to occur in the clinical form of keloids or hypertrophic scars.

If a clean-cut incision with a razor sharp instrument is made without the introduction of pathogenic bacteria, the keloid growth is not liable to result, for there is not the excess transudation of tissue fluids in the wound area. Furthermore, because of the close proximity of the tissues in such an incision, there is little space for transudate to collect and remain stagnant. For these reasons, such a wound will heal rapidly without keloid formation. This is especially true if the vitamin c intake is adequate and the circulation in the wound area is kept at a low temperature by ice packs.[23]

## SUPPORTIVE EXPERIMENTS ON PATIENTS WITH KELOIDS

As has been mentioned before, evidence has been collected to show that scars, *per se*, are not entirely permanent,[24] for there

seems to be at least some permanent reduction in the size of the scar tissue when the vasoconstrictor material was employed parenterally over a long period of time. (The vasoconstricting material is a special fraction of liver extract prepared by the Eli Lilly Laboratories of Indianapolis according to Marshall's technic.) The reduction in the size of the keloid could be noted within fifteen minutes if the vasoconstricting substance was injected intradermally in the immediate proximity of the keloid. No intrakeloidal injections were used as it was believed that the collagenous material would plug the fine needle. Following injections into the skin, fine white linear streaks from 1 mm. to 5 mm. in length and from 1 mm. to 2 mm. in width could be seen with a radius of 15 to 20 cm. of the site of injection denoting vasoconstriction of skin capillaries. This material appears to have a selective vasoconstricting effect on the skin capillaries since no constitutional effects such as increased blood pressure or tachycardia have been seen following either subcutaneous or intradermal injections. In this respect, it differs markedly from the action of adrenalin or ephedrine.

Since the clinical and microscopic studies have demonstrated the presence of a relatively abundant amount of tissue fluid present in hypertrophic scars and keloids, this experimental work has shown several points of interest. It has been shown, for example, that vasoconstriction of the terminal blood vessels of the skin tends to remove the stains which accompany infection with the resultant keloid formation. Our studies have shown that the induration, and hyperemia, tend to improve when the vasoconstrictor material reaches the involved skin areas. Hence, the blanching effect of this material is the result of the vasoconstricting action from our experimental material.

By parenteral injection this therapeutic effect is generalized, in that by absorption the material reaches such areas as the back, chest, face, and arms of the patients. Five patients who have had weekly parenteral injections over a period of one and one-half years, have presented a decided clinical improvement of the keloidal areas.

The question arose as to the advisability of injecting this vasoconstrictor material directly into the scar tissue, since it was reasoned that the therapeutic effect may be greater by implanting the material directly into the keloids and hypertrophic scars.

It happened that a new case became available for such an experiment. This young man had two large, separate keloids at the inferior portion of the left mandibular region. He had, also, the typical "washboard" keloids as the result of acne vulgaris some years ago. He had been given nine subcutaneous injections of $\frac{1}{20}$ cc. of our experimental fraction which was derived from liver extract. The therapeutic periods were spaced at weekly intervals. During these nine weeks, the mandibular keloids had "shrunk" about one-half an inch in length and about one-fourth inch in width. They were softer in consistency and had become somewhat blanched, for previously they were markedly hyperemic. The sternal keloids in this case exhibited identical changes.

Several direct injections were performed on the upper mandibular keloid, which was the larger neoplasm. No injections were made on the lower mandibular keloid. These treatments were performed at weekly intervals.

As each injection of the upper keloid was performed, it was noted that the hypodermic needle (Becton-Dickinson No. 26 gauge) met with definite resistance because of the resistance which was caused by the apparent fibrotic keloid mass. One-twentieth cc. of our experimental fraction was injected with considerable difficulty, and care was taken not to push the needle into the tissue below the neoplasm.

Due to the trauma, which was caused by this injection, the keloid became markedly hyperemic and this was present for about three minutes, after which time, the neo-

plasm was noted to blanch. This was rather marked in extent after five minutes following the time of injection. The inferior keloid did not show the preliminary hyperemia, but it began to blanch in about the same time.

It was observed that the borders showed a marked blanching, and furthermore, as time progressed, these borders seemed to lose their fluid content to some degree. This was tested by using a pencil point for such palpation, which produced a definite pitting phenomenon which was not evident before the injection was administered.

There was an escape of straw-colored fluid at the site of the injection area. In order to determine whether this exudate was our injected material or escaping tissue fluid, this exudate was placed in capillary tubes which were broken at minute intervals to determine the presence, if any, of a clotting phenomenon. We noted its occurrence in five minutes. Evidently, this escaping fluid was "tissue juice," for it showed the presence of a "fibrin veil."

As time progressed, both keloids showed a definite flattening of their borders, so that the skin follicles with their protruding hairs were discernable. These were not present before the injection. Furthermore, a marked multiple "creasing" effect occurred in the dome of the keloids as the pressure of the fluid escaped or was partially absorbed through the vasoconstricting action of the injected experimental material. The escape of the tissue fluid through the puncture wound was very small in amount and the fluid which was lost in such a manner was insignificant and could not account for the "settling" of the neoplasms. Furthermore, the inferior neoplasm showed the same shrinking effect and no injection was made in it. Hence, it could be assumed that the vasoconstriction action of the injected fraction was the most important cause for the partial collapse of these keloids. The loss of the tissue fluid was also noted in the sternal keloids, since corregations appeared on the surface of these "washboard keloids."

## DEDUCTIONS FROM THESE EXPERIMENTAL RESULTS

These observations were confirmed with similar experiments, which were performed in a similar manner, in the same individual.

Since it is known that vasoconstriction of the peripheral arterial buds will have the tendency to improve a localized edema of the tissue, it is our assumption that these keloids contain a considerable amount of transudate. When vasoconstriction is produced, as with our experimental material, this tends to lessen stasis in such areas with the actual observation of a shrinking process in the neoplasm which followed the improvement in the tissue edema.

To put these results another way, there is now evidence that keloids are not totally composed of connective tissue. There is an abundant amount of tissue fluid transudate which probably has been produced by a pathological change in the hydrostatic and the osmotic pressures of the involved areas. As the edema displaces the tissue spaces, connective tissue is formed, but the edema persists to a considerable extent.

However, by at least partially reversing this pathological process, by peripheral vasoconstriction with the use of our experimental injected fraction, which produces the same final clinical effects whether introduced subcutaneously or directly into the neoplasm, this stasis is relieved with a shrinkage of the keloids in various portions of the body.

## SUMMARY

1. The psychological importance of these new growths is emphasized.

2. The rôle which vasoconstriction plays in the governing of tissue fluid tension is reviewed.

3. The microscopic pathology of keloids, hypertrophic scars, and similar entities is discussed, along with the various clinical aspects of each neoplasm.

4. The physiological phenomena are reviewed which produce the tissue fluids.

A description is given of the production of tissue edema.

5. The peculiar anatomy of the skin circulation is described.

6. The authors have reviewed the results of tissue fluid extravasation in various diseases and the nature of the pathophysiology which results.

7. This phenomenon is discussed when it occurs in the tissue spaces of the skin.

8. The relationship of the formation of skin edema is reviewed in view of its probable relationship to the formation of connective tissue and the formation of keloids and related neoplasms.

9. The authors' experiments for the partial reduction of skin edema, in a case of keloidosis, are presented. With decrease in the local transudate, there resulted a shrinking of the keloids which was discernible clinically.

10. Peripheral vasoconstriction seems to produce a reduction in the firmness of keloids by the resultant reduction in the localized skin edema which apparently is present in keloids.

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# CHLOROPHYLL*

## AN EXPERIMENTAL STUDY OF ITS WATER SOLUBLE DERIVATIVES IN WOUND HEALING

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THE problem of wound healing becomes of paramount importance in time of war. In the intervals between wars somewhat desultory and fragmentary investigations continue to be carried on in this general field, but the bulk of research is directed at other more spectacular issues of current interest. The prosaic, commonplace problem of the repair of wounds, like the proverbial poor relative, is always with us, and is dismissed as one of little interest or likelihood of acclaim. In the past two or three years, however, medical literature has devoted a very considerable percentage of its space to studies relating to the treatment of burns and wounds. It is obviously impossible for any one individual to familiarize himself with more than a small fraction of this literature, much less carry out in his own practice the thousand and one recommendations for the treatment of such injuries.

For that reason, it is well to adopt a conservative and frankly skeptical point of view regarding the relatively extravagant claims of each enthusiastic contributor to the rapidly growing chemotherapeutic armamentarium available for the treatment of burns and other traumatic injuries. Such publications as the recent National Research Council's Military Surgical Manual No. 5[20] reflect this sane approach. Likewise, the contributions of Bowers,[6] Whipple,[28] Waugh,[27] Harkins[16] and Brush and Lam[7] to this field present a most encouraging and hopeful attitude. They all stress the basic physiological principles involved in the healing process which have been all too frequently disregarded until comparatively recently, although Carrel[9] and his associates over twenty-five years ago recognized their importance and evolved certain fundamental laws in respect to wound healing.

These earlier investigators developed a mathematical formula of geometric progression in respect to the estimated time required for repair of any wound, based on its surface area. They recognized that larger wounds tended to heal more rapidly than small ones; that the repair phenomenon was influenced by age, tissues from older individuals requiring longer to heal than those of children. They noted the so-called "lag" or latent period between the time the injury occurred and the beginning repair phenomenon, which is still credited to the biophysical changes associated with the inflammatory exudative phase of the process. And it was Carrel who evolved the "trephone" theory of enzymatic growth stimulating factors being produced through tissue destruction or inflammatory cell metabolism. "Laudable pus" was explained on this same basis, as a necessary irritant to induce cell proliferation, for in its absence, repair was retarded or ceased altogether.

Menkin's[19] now classical studies on inflammation have gone a long way to explain these various phenomena by sound physicochemical theory; stressing the importance of the hydrogen ion concentration of the tissues, the rôle of fibrinolysin, the place of the euglobulin fraction of the exudate (necrosin) which appears to be responsible for the subsequent course of events following the initial injury, and the

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value of the pseudoglobulin chemotactic fraction (leukotaxin). Tissue culture studies have emphasized the importance of these metabolic or breakdown enzymic products of tissue injury as evidenced by the routine use of such tissue extracts as splenic extract, embryonic tissue juice, "leucocytic cream" and the like as an integral part of the usual media employed.

Currently, a good deal of interest has been shown in a product devised by Sperti[25] and his associates for the treatment of minor burns and injuries, which they have termed "Bio-dyne" ointment. Its use is predicated on the same fundamental theory that cells liberate a growth stimulating factor when injured or destroyed. These workers have employed yeast cells injured or destroyed by ultraviolet irradiation as the source of their growth stimulating factor or "hormone." Cook and Fardon[11] and Nutini[21] from the same laboratories review the concept of wound hormones from the time of Virchow's "formative stimulus" in 1858, and stress the evidence which they have obtained experimentally of the production by injured cells of substances which "promote the proliferation and metabolism of living cells."

In our own studies we have noted the marked "boosting" effect of leucocytic cream extract on cell growth in tissue cultures.[24] We believe the evidence is convincing that some substance or substances derived from injured or dead tissue or inflammatory cells are the chief factors responsible for initiating the reparative phase of any local destructive process regardless of the etiologic agent producing the immediate injury. It appears equally apparent that the so-called lag period before repair ordinarily begins is dependent upon the catabolic cell changes resulting from the injury. Thus, the entire exudative and reparative phases of tissue injury might be thought of in terms of a series of complicated chemical reactions which undoubtedly in due course of time can be reduced to mathematical equations. One gains the impression that the reparative phase of wound healing is dependent upon the accumulation of an adequate amount of the growth stimulating factors to neutralize and hold in check the catabolic phenomena. Whether this mechanism is primarily dependent upon the liberation of these stimulating factors quantitatively in respect to the number of cells injured or destroyed, or whether these products are actually enzymes or "hormones" capable of propagation interstitially in the tissue fluids is uncertain and perhaps not strictly pertinent to the problem at this time.

In any event, therapeutic efforts to reduce this lag period either by diminishing the catabolic phase or by stimulating the anabolic, proliferative processes are the objective desideratum of all investigators. It is apparent that gross bacterial infection delays healing, so that one aim of any treatment is to produce bacteriostasis. At the same time it is not at all certain that complete bacterial sterilization is either necessary or even advisable, for it is quite possible that minimal saprophytic surface contamination may augment the reparative proliferation by supplementing the necessary stimulating factor with the breakdown of the bacteria themselves. It is equally obvious that a poor blood supply as occurs in chronic indolent ulcers, especially those associated with *x*-ray burns or on a varicose vein basis is another important factor. In these latter conditions, a slowly developing fibrosis with resultant hyalinization of the collagen plays an important part in the retardation of the repair process through further cutting down the blood supply.

With these theoretical considerations in mind, we have joined the vast group of investigators in this field in an attempt to add our contribution toward the solution of the problem. In view of the considerable discussion which has been raised in the past few years regarding the possible place of chlorophyll in our therapeutic armamentarium, we have undertaken a study on wound healing using water soluble chlorophyll preparations made up in various ways

(as solutions, jellies, and ointments) in the treatment of experimentally induced burns and wounds in rats, guinea pigs, rabbits and dogs, as well as in a limited number of clinical cases.

In order properly to evaluate the value of chlorophyll* therapeutically, a considerable number of other agents were studied in identical manner, using standard surgically induced wounds or dry heat burns. The agents† employed were the following:

1. Chlorophyll—0.2 per cent alkaline saline solution (pH 7.3–7.8)
2. Chlorophyll—0.2 per cent acid buffered solution (pH 6.6–6.8)
3. Chlorophyll—lanoline base ointment—0.5, 1.0, 2.0 and 3.0 per cent
4. Chlorophyll—petrolatum-cholesterol base ointment—2.0 per cent
5. Chlorophyll—hydrophilic base jelly—1.0 per cent
6. "Bio-dyne" ointment
7. Vitamin B complex ointment—1 per cent
8. Vitamin C ointment—0.1 per cent
9. Vitamin D (cod-liver oil) ointment
10. Methionine ointment—0.05 per cent
11. Castilian malva used as 10 per cent infusion
12. Sulfanilamide (powdered)
13. Sulfathiazole (powdered)
14. Sulfathiazole ointment—5 per cent
15. Sulfadiazine spray—2 per cent
16. Scharlach R ointment
17. Tetrodine dusting powder—6 per cent iodine
18. Controls—untreated

* Whenever the term "chlorophyll" is used in these studies, the water-soluble derivatives are meant, the term "chlorophyll" being used solely for the sake of brevity.

† Acknowledgments: *Agents No. 1 to 5*—The experimental aqueous soluble chlorophyll products have been generously supplied us through the courtesy of the Rystan Company of New York, sole appointee of the Lakeland Foundation of Chicago, in accordance with the regulations of the Federal Food, Drug and Cosmetic Act relative to therapeutic products. *Agent No. 6*—The Bio-dyne ointment was kindly supplied us by the Sperti Laboratories of Cincinnati. *Agent No. 9*—The cod liver oil ointment (Gadamont—E. L. Patch Co.) was purchased in the open market. *Agent No. 10*—The methionine was supplied for experimental study by Merck & Company of Rahway, N.J., and the other Merck products used were made available through our own pharmacy. *Agent No. 11*—The Castilian Malva was supplied us by the Upjohn Company of Kalamazoo, Michigan. *Agent No. 17*—The Tetrodine dusting powder was supplied us by the Tyler Laboratories of Brooklyn, N.Y.

## PROCEDURE

In the smaller animals—rats, guinea pigs and rabbits—under nembutal anesthesia, symmetrical, roughly circular, 1.0 cm. areas of skin were excised from the thorax, abdomen or back, after first shaving and painting the operative field with tetrodine. In the rats, guinea pigs and rabbits, a single pair of lesions was produced. As in Clark's recently reported studies,[10] the left side was regularly used as the control, the right side for the experimental treatment. In the dogs it was possible to make as many as four pairs of 2.5 cm. lesions. In these animals the anterior pair of lesions were used as controls, the left, right and posterior pairs as the experimental areas. The procedure varied somewhat in this group inasmuch as it has been impossible to obtain dogs in the numbers desired. Thus as many as three test agents might be employed simultaneously on the same animal. This is open to the criticism that the amount of systemic reponse from absorption of the various agents is difficult to evaluate and there might therefore be a cumulative effect. However, it is believed that this criticism can be satisfactorily answered, as in no instance was such multiple testing employed without also testing a control animal in which only a single agent was used. The entire method is relatively crude but follows the pattern employed by other investigators in this field such as Whipple,[28] Thompson[26] and Ravdin, Harkins,[16] Brush and Lam,[7] Clark,[10] Boehringer,[5] Buergi[8] and Gruskin.[14] It is dependent upon observing the difference in the rate of healing of standard experimentally induced wounds in a sufficient number of cases to render the results statistically significant.

In the larger animals—dogs—a technic was evolved whereby wounds identical in size could be produced by mounting a Bard Parker knife blade in an adjustable arm attached to a spindle. The spindle has three pinpoints in its foot which hold the instrument in position on the skin surface

with but slight pressure. By revolving the arm, a perfect circle can be cut through the skin and subcutaneous tissues down to the fascial layers. This disc of skin can then be readily excised sterilely leaving a clean-based circular defect of whatever diameter is desired—in these particular animals, 2.5 cm. A cork or aluminum ring somewhat larger than the lesion is then cemented to the skin with celloidin, lucite or Johnson & Johnson's liquid adhesive. This enables us to treat the lesions individually with no danger of the test agent contaminating the control area. The test agent is introduced generously on a small piece of double-thickness coarse meshed surgical gauze cut to fit just inside the protecting ring. The intervening areas are loosely packed with crumpled gauze and a binder made of light weight duck applied over the whole trunk. This is held in place by cutting two holes for the forelegs, overlapping the two ends of the binder and sewing them snugly over the back of the animal with interrupted stitches. To protect the field further from harm, a wide collar (6 to 8 inch radius) made of two layers of corrugated cardboard with the corrugations at right angles to each other to prevent its buckling is placed around the dog's neck, and each dog put in an individual cage. Even with these precautions, an occasional dog may get his dressing off, apparently by persistent rubbing against the cage, but in general, the method seems the most satisfactory we have been able to discover.

By this technic, it is comparatively easy to redress the wounds as desired, usually every second or third day. At each examination the extent of healing is recorded by measuring the remaining unepithelialized area, either by using Brush and Lam's technic of actually tracing the edges of the wound on cellophane or by the use of calipers in three transverse directions. It is not believed that planigraphy is necessary, as our chief concern is in respect to the comparative time required to secure complete healing in each case.

This method has the advantage, as Clark has emphasized, of permitting regulated infection to be introduced into the experimental field without much likelihood of contamination of the control area, and thereby making it possible to test the bactericidal or bacteriostatic effect of various agents *in vivo* in a somewhat crude, but at least, comparable manner. The second group of experiments reported here deals with this phase of the problem.

Finally, a similar set of experiments was carried out in which standardized wounds, produced by dry heat, were studied in respect to their healing characteristics. For this purpose, steel cylinders about 2.5 cm. in length and of the diameters desired—2.5 and 5.0 cm., respectively—were hollowed out at one end to permit introducing a flanged tube. This tube serves the double purpose of acting as a handle, and of permitting the introduction of a thermometer into the hollow cylinder. The hollow cavity is filled with mercury to prevent any insulation in respect to the thermometer. The apparatus is then heated to the desired temperature and applied to the skin surface without other pressure than its own, known weight for varying lengths of time, depending on the degree of burn desired. From long experience we have found that there is very little heat loss—roughly 5°C. for each fifteen seconds of application with the smaller, and about 2°C. loss with the larger cylinder over the same time period. For practical purposes, we have found 250°C. applied for thirty seconds gives a very satisfactory mild third degree burn in dogs. As in the case of the surgically produced wounds the lesions are uniform and completely comparable for the purposes of a study such as this. The skin sloughs off in four to five days, leaving a clean-based, circular, ulcerated surface. By protecting the burned areas in the same way as in the preceding surgically induced wounds they can be kept free of bacterial contamination or not, as desired, and topical application of any of the medicaments under study can be carried out satisfactorily.

The experiments included in this report fall into three main groups as already indicated: (1) The healing of experimentally produced clean surgical wounds; (2) the healing of experimentally infected surgical wounds, and (3) the healing of experimentally induced dry heat burns.

TABLE I
STATISTICAL SUMMARY OF EXPERIMENTAL MATERIAL

| | No. of Animals | No. of Lesions | No. Control Lesions | No. Test Lesions |
|---|---|---|---|---|
| Group I | | | | |
| Sterile Wounds | | | | |
| Experiments 1–18 Rats | 108 | 216 | 114 | 102 |
| 19–36 Guinea pigs | 108 | 216 | 114 | 102 |
| 37–54 Rabbits | 78 | 156 | 82 | 74 |
| 55–72 Dogs | 76 | 608 | 164 | 444 |
| Group II | | | | |
| Infected Wounds | | | | |
| Experiments 73–90 Guinea pigs | 208 | 416 | 212 | 204 |
| 91–108 Dogs | 36 | 254 | 84 | 170 |
| Goup III | | | | |
| Third Degree Burns | | | | |
| Experiments 109–126 Dogs | 48 | 384 | 108 | 276 |
| Totals | 662 | 2,250 | 878 | 1,372 |

In each of these three main groups there are eighteen separate experiments with each type of animal used, based on the seventeen preparations under study plus a supplementary control group. In the small animals a single test area has been used with a corresponding control area on the opposite side of the animal. In the dogs eight lesions have been produced, two of which have served as controls, and six as test areas. Table I shows in summary form the statistical data relating to the number of experiments, number of animals used, the number of control lesions and the number of experimental lesions tested.

The seventeen preparations tested can be reduced in actual number to eight, by combining the several chlorophyll, vitamin and sulfone compounds as group products. Justification for such simplification of the accumulated data is seen in the similarity of results within these related group preparations. In the simple, clean, wound healing experiments, identical studies were carried out on rats, guinea pigs, rabbits and dogs. In Group II, consisting of experimentally induced infected wounds only guinea pigs and dogs were used, and in the Group III burn experiment dogs were found to be much more satisfactory to work with than any of the smaller animals.

TABLE II
1 PER CENT CHLOROPHYLL IN HYDROPHILIC JELLY BASE
Time Required for Healing 1.0 Cm. Sterile, Surgically Produced Wounds, Expressed in Days

| Identification | | Control Area | Test Area | Summary |
|---|---|---|---|---|
| Rat | 31 | 12 | 8 | |
| | 32 | 16 | 12 | Accelerated....4—66.7% |
| | 33 | 16 | 10 | Unaffected.....2—33.3% |
| | 34 | 14 | 14 | Delayed.....0— 0.0 |
| | 35 | 10 | 8 | |
| | 36 | 14 | 14 | |
| Guinea Pig | 31 | 16 | 10 | |
| | 32 | 18 | 10 | Accelerated....5—83.3% |
| | 33 | 14 | 14 | Unaffected.....1—16.7% |
| | 34 | 14 | 8 | Delayed.....0— 0.0 |
| | 35 | 12 | 10 | |
| | 36 | 14 | 10 | |
| Rabbit | 31 | 16 | 12 | |
| | 32 | 14 | 14 | Accelerated....5—83.3% |
| | 33 | 16 | 10 | Unaffected.....1—16.7% |
| | 34 | 10 | 8 | Delayed.....0— 0.0 |
| | 35 | 16 | 12 | |
| | 36 | 12 | 8 | |
| Total | | 254 | 192 | Accelerated...14—77.7% |
| | | | | Unaffected.....4—22.3% |
| Average | | 14.1 | 10.6 | Delayed.....0— 0.0 |

## EXPERIMENTAL RESULTS

The experimental results are probably best presented for consideration through the following series of tables in which the statistical data have been assembled for comparative study and analysis. Such additional comment or discussion as seems pertinent to an understanding of the figures is included. It does not seem necessary or even advisable to include the individual protocols of all the experiments as the useful information is adequately summarized in the combined tables. However, representative protocols of a couple of typical experiments are presented to illustrate the

method whereby the data as a whole were obtained for statistical analysis. (Tables II and III.)

In the first group of experiments, which deals with the healing of clean, surgically produced wounds, the complete data will be found summarized in Table IV, as these relate to 1.0 cm. wounds in small animals, and to larger 2.5 cm. wounds in dogs, respectively.

Not only is the percentage of such accelerated healing notably better than with any of the other agents studied, but the average time interval required for complete healing decreased by 3.5 days (from 14.1 to 10.6 days) a figure just short of 25 per cent (24.9 per cent). In a considerable number of the animals the differential time interval was as much as six to eight days which is a very real difference. When

TABLE III

I PER CENT CHLOROPHYLL IN LANOLINE OINTMENT BASE

TIME REQUIRD FORE HEALING OF 2.5 CM. STERILE, SURGICALLY PRODUCED WOUNDS IN DOGS EXPRESSED IN DAYS

| | Dog No. | Total No. Lesions | No. of Control Lesions | No. of Test Lesions | Time of Healing in Days | | | | | | | | Average | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Control | | Test Areas | | | | | | Control | Test |
| Experiment No. 57 Test animals. | 9 | 8 | 2 | 6 | 16 | 18 | 10 | 8 | 8 | 12 | 10 | 10 | 17 | 9.6 |
| | 10 | 8 | 2 | 6 | 14 | 12 | 12 | 12 | 14 | 14 | 12 | 14 | 13 | 13.0 |
| | 11 | 8 | 2 | 6 | 16 | 14 | 12 | 12 | 10 | 12 | 14 | 12 | 15 | 11.6 |
| | 12 | 8 | 2 | 6 | 12 | 12 | 12 | 14 | 12 | 12 | 20* | 22* | 12 | 15.3 |
| | 13 | 8 | 2 | 6 | 16 | 14 | 10 | 12 | 12 | 12 | 10 | 12 | 15 | 11.3 |
| | 14 | 8 | 2 | 6 | 14 | 14 | 8 | 12 | 10 | 12 | 14 | 12 | 14 | 11.3 |
| Experiment No. 72 Control animals. | 69 | 8 | 8 | .. | 12 | 14 | 14 | 12 | 14 | 14 | 12 | 14 | 13.2 | |
| | 70 | 8 | 8 | .. | 16 | 14 | 18 | 14 | 16 | 16 | 18 | 14 | 15.7 | |
| | 71 | 8 | 8 | .. | 14 | 16 | 12 | 12 | 12 | 16 | 14 | 14 | 13.7 | |
| | 72 | 8 | 8 | .. | 12 | 12 | 14 | 16 | 14 | 12 | 12 | 14 | 13.2 | |
| Total..... | 10 | 80 | 44 | 36 | .. | .. | .. | .. | .. | .. | ... | ... | 14.0 | 12.1 |

*Summary:* Healing accelerated—4 animals or 67.0%
" unaffected —1 animal or 16.5%
" delayed —1 animal or 16.5%

* Infected.

In summary, we note that 67 per cent of all the wounds treated by one or another preparation of chlorophyll healed more rapidly than their controls. This percentage varies from 55 per cent in the case of the acid buffered aqueous solution to 75 per cent with the 1 per cent hydrophylic base jelly as a vehicle. Referring to Table II we see that, using the hydrophilic jelly preparation, as high as 83.3 per cent of the wounds in guinea pigs and rabbits showed such acceleration in the healing process. the reading is only a matter of two days, (the routine time interval between redressing and examining the wounds), as Brush and Lam have emphasized, one is justified in querying any actual effect of the agent under study. But when the time required for healing is reduced by one-fourth in from two-thirds to three-quarters of a series of over four hundred lesions, it would seem to indicate that chlorophyll does cause some biologic response in respect to stimulating cell growth which can be put to a useful

purpose in the many problems associated with wound healing.

This stands out particularly prominently if one summarizes the results obtained with various vitamin and sulfone compounds (Table v), as well as with the various miscellaneous agents tested by ourselves and by Brush and Lam in which it can be seen at a glance that little or no favorable effect upon the rate of healing was obtained, and indeed, in a not insignificant percentage of the wounds there was an appreciable retardation noted in the rate of healing. As a matter of collateral interest, it should be mentioned that where actual delay in healing occurred in the animals treated with chlorophyll there was secondary infection present. That aspect of the problem is more clearly seen in the second group of experiments in which infection was introduced into the wounds. It has already been brought out in another paper of this series[24a] that chlorophyll is not of itself actually bactericidal, but that it does exert a definite bacteriostatic effect *in vitro*, apparently through its oxidative action. Its mode of action *in vivo* is still obscure, but it is believed that interference with fibrinolysin production and its growth stimulating capacity are also of importance.

In the second group of experiments which deals with artificially infected surgically produced wounds, the data in summary form are presented in Table VI. Here again, it is to be noted that almost the same relative acceleration in healing is noted in the chlorophyll group as compared with the other test agents as in the uninfected series of cases. However, in the group of miscellaneous agents, several of which are more or less antiseptic in their action, there is a definite shift in the picture toward more rapid healing with a corresponding drop in the delayed healing percentage figures. This is particularly striking in the case of "Tetrodine," a stable aqueous

TABLE IV

HEALING OF STERILE, SURGICALLY INDUCED WOUNDS

| | Rats | | | | Guinea-Pigs | | | | Rabbits | | | | Dogs | | | | Summary | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Healing | | | | Healing | | | | Healing | | | | Healing | | | | Healing | | | | | |
| | No. Animals | Accelerated | Unaffected | Delayed | No. Animals | Accelerated | Unaffected | Delayed | No. Animals | Accelerated | Unaffected | Delayed | No. Animals | Accelerated | Unaffected | Delayed | Total Number of Animals | Number Accelerated | Accelerated Per Cent | Number Unaffected | Unaffected Per Cent | Number Delayed | Delayed Per Cent |
| Chlorophyll—alkaline solution | 6 | 4 | 1 | 1* | 6 | 3 | 2 | 1* | 4 | 2 | 1 | 1 | 4 | 3 | 1 | 0 | 20 | 12 | 60 | 5 | 25 | 3 | 15 |
| Chlorophyll—acid solution | 6 | 4 | 2 | 0 | 6 | 4 | 1 | 1* | 4 | 1 | 3 | 0 | 4 | 2 | 2 | 0 | 20 | 11 | 55 | 8 | 40 | 1 | 5 |
| Chlorophyll—lanoline ointment | 6 | 4 | 2 | 0 | 6 | 4 | 2 | 0 | 6 | 4 | 1 | 1* | 6 | 4 | 1 | 1* | 24 | 16 | 67 | 6 | 25 | 2 | 8 |
| Chlorophyll—cholesterol ointment | 6 | 5 | 1 | 0 | 6 | 4 | 2 | 0 | 6 | 4 | 2 | 0 | 6 | 5 | 1 | 0 | 24 | 18 | 75 | 6 | 25 | 0 | 0 |
| Chlorophyll—hydrophilic jelly | 6 | 4 | 2 | 0 | 6 | 5 | 1 | 0 | 6 | 5 | 1 | 0 | 6 | 4 | 2 | 0 | 24 | 18 | 75 | 6 | 25 | 0 | 0 |
| Total chlorophyll | 30 | 21 | 8 | 1* | 30 | 20 | 8 | 2 | 26 | 16 | 8 | 2 | 26 | 18 | 7 | 1 | 112 | 75 | 67 | 31 | 27.5 | 6 | 5.5 |
| Bio-dyne | 6 | 2 | 3 | 1* | 6 | 2 | 4 | 0 | 4 | 2 | 2 | 0 | 4 | 1 | 3 | 0 | 20 | 7 | 35 | 12 | 60 | 1 | 5 |
| Vitamin B ointment | 6 | 1 | 4 | 1 | 6 | 0 | 6 | 0 | 4 | 1 | 3 | 0 | 4 | 0 | 3 | 1* | 20 | 2 | 10 | 16 | 80 | 2 | 10 |
| Vitamin C ointment | 6 | 2 | 3 | 1* | 6 | 1 | 4 | 1 | 4 | 0 | 4 | 0 | 4 | 1 | 3 | 0 | 20 | 4 | 20 | 14 | 70 | 2 | 10 |
| Vitamin D ointment | 6 | 2 | 4 | 0 | 6 | 2 | 4 | 0 | 4 | 1 | 2 | 1* | 4 | 0 | 3 | 1 | 20 | 5 | 25 | 13 | 65 | 2 | 10 |
| Methionine ointment | 6 | 3 | 2 | 1 | 6 | 2 | 4 | 0 | 4 | 2 | 2 | 0 | 4 | 1 | 3 | 0 | 20 | 8 | 40 | 11 | 55 | 1 | 5 |
| Castilian malva infusion | 6 | 1 | 4 | 1* | 6 | 2 | 3 | 1* | 4 | 1 | 3 | 0 | 4 | 2 | 2 | 0 | 20 | 6 | 30 | 12 | 60 | 2 | 10 |
| Sulfanilamide powder | 6 | 0 | 2 | 4 | 6 | 0 | 3 | 3 | 4 | 0 | 2 | 2 | 4 | 0 | 1 | 3 | 20 | 0 | 0 | 8 | 40 | 12 | 60 |
| Sulfathiazole powder | 6 | 0 | 3 | 3 | 6 | 0 | 2 | 4 | 4 | 0 | 3 | 1 | 4 | 0 | 2 | 2 | 20 | 0 | 0 | 10 | 50 | 10 | 50 |
| Sulfathiazole ointment | 6 | 0 | 2 | 4 | 6 | 1 | 3 | 2 | 4 | 0 | 1 | 3 | 4 | 0 | 2 | 2 | 20 | 1 | 5 | 8 | 40 | 11 | 55 |
| Sulfadiazine spray | 6 | 1 | 4 | 1 | 6 | 0 | 4 | 2* | 4 | 1 | 1 | 2 | 4 | 0 | 1 | 3 | 20 | 2 | 10 | 10 | 50 | 8 | 40 |
| Scharlach R ointment | 6 | 2 | 3 | 1* | 6 | 3 | 3 | 0 | 4 | 1 | 3 | 0 | 4 | 1 | 2 | 1 | 20 | 7 | 35 | 11 | 55 | 2 | 10 |
| Tetrodine powder | 6 | 1 | 3 | 2 | 6 | 0 | 4 | 2 | 4 | 0 | 2 | 2 | 4 | 0 | 3 | 1 | 20 | 1 | 5 | 12 | 60 | 7 | 35 |
| Control | 6 | .. | .. | .. | 6 | .. | .. | .. | 4 | .. | .. | .. | 2 | .. | .. | .. | 18 | | | | | | |
| Totals | 108 | .. | .. | .. | 108 | .. | .. | .. | 78 | .. | .. | .. | 76 | .. | .. | .. | 370 | | | | | | |

* Infection.

preparation of iodine, as well as in the various sulfone compound treated lesions. Of the three sulfa drugs tested in this respect, sulfadiazine in a 2 per cent spray seemed the most effective in controlling infection, and thereby, indirectly hastening repair. Bio-dyne, here as in the clean wounds appeared to have an appreciable accelerating effect from the percentage standpoint, but actually this difference was hard to evaluate, because it was only by a matter of a couple of days in the majority of cases. Scharlach R ointment in our hands had little or no effect on the rate of growth. This independently confirmed the report by Brush and Lam. The same inconclusive evidence was obtained in respect to the use of methionine and the various vitamin ointments as well as Castilian malva infusion preparations so far as their effect upon wound healing is concerned. (Table VII.)

In the third group of experiments which were designed to show the healing effect of topical applications of various agents on standard dry heat burns of varying size and

TABLE V

RATE OF HEALING OF EXPERIMENTAL SURGICAL WOUNDS

| Test Agent | Accelerated, Per Cent | Unaffected, Per Cent | Delayed, Per Cent |
|---|---|---|---|
| Chlorophyll preparations | 67.0 | 27.5 | 5.5 |
| Vitamin ointments | 18.4 | 71.6 | 6.0 |
| Sulfa compounds | 3.8 | 45.0 | 51.2 |
| *Miscellaneous | 19.4 | 55.1 | 25.5 |

* See Table IV this article and Table II in Brush and Lam's (loc. cit.).

TABLE VI

HEALING OF SURGICALLY INDUCED WOUNDS, EXPERIMENTALLY INFECTED WITH 0.5 CC. OF A MIXTURE OF STAPHYLOCOCCUS AUREUS (STRAIN C-209) AND STREPTOCOCCUS HEMOLYTICUS (LANCEFIELD GROUP A STRAIN C-203) TWENTY-FOUR HOUR BROTH CULTURES

| Test Agent | Guinea Pigs | | | | Dogs | | | | | Summary | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Healing | | | | | Healing | | | | Healing | | | | | |
| | No. Animals | Accelerated | Unaffected | Delayed | No. Animals | No. Lesions Treated | Accelerated | Unaffected | Delayed | Total Lesions | Accelerated | Per Cent | Unaffected | Per Cent | Delayed | Per Cent |
| Chlorophyll—alkaline solution | 12 | 8 | 2 | 2 | 2 | 4 | 3 | 1 | 0 | 16 | 11 | 69 | 3 | 19 | 2 | 12 |
| Chlorophyll—acid solution | 12 | 9 | 2 | 1 | 2 | 4 | 3 | 1 | 0 | 16 | 12 | 75 | 3 | 19 | 1 | 6 |
| Chlorophyll—lanoline ointment | 12 | 6 | 4 | 2 | 2 | 6 | 4 | 1 | 1 | 18 | 10 | 55 | 5 | 28 | 3 | 17 |
| Chlorophyll—cholesterol ointment | 12 | 5 | 6 | 1 | 2 | 6 | 4 | 2 | 0 | 18 | 9 | 50 | 8 | 44 | 1 | 6 |
| Chlorophyll—hydrophilic jelly | 12 | 7 | 4 | 1 | 2 | 6 | 5 | 1 | 0 | 18 | 12 | 67 | 5 | 26 | 1 | 7 |
| Total chlorophyll | 60 | 35 | 18 | 7 | 10 | 26 | 19 | 6 | 1 | 86 | 54 | 63 | 24 | 28 | 8 | 9 |
| Bio-dyne ointment | 12 | 4 | 6 | 2 | 2 | 12 | 5 | 6 | 1 | 24 | 9 | 38 | 12 | 50 | 3 | 12 |
| Vitamin B ointment | 12 | 2 | 10 | 0 | 2 | 12 | 3 | 8 | 1 | 24 | 5 | 21 | 16 | 67 | 3 | 12 |
| Vitamin C ointment | 12 | 1 | 10 | 1 | 2 | 12 | 2 | 9 | 1 | 24 | 3 | 13 | 19 | 79 | 2 | 8 |
| Vitamin D ointment | 12 | 3 | 7 | 2 | 2 | 12 | 3 | 9 | 0 | 24 | 6 | 25 | 16 | 67 | 2 | 8 |
| Methionine ointment | 12 | 3 | 6 | 3 | 2 | 12 | 4 | 6 | 2 | 24 | 7 | 29 | 12 | 50 | 5 | 21 |
| Castilian malva infusion | 12 | 2 | 8 | 2 | 2 | 12 | 4 | 7 | 1 | 24 | 6 | 25 | 15 | 63 | 3 | 12 |
| Sulfanilamide powder | 12 | 4 | 6 | 2 | 2 | 12 | 3 | 8 | 1 | 24 | 7 | 29 | 14 | 58 | 3 | 13 |
| Sulfathiazole powder | 12 | 3 | 6 | 3 | 2 | 12 | 2 | 7 | 3 | 24 | 5 | 21 | 13 | 54 | 6 | 25 |
| Sulfathiazole ointment | 12 | 3 | 7 | 2 | 2 | 12 | 4 | 6 | 2 | 24 | 7 | 29 | 13 | 54 | 4 | 17 |
| Sulfadiazine spray | 12 | 4 | 7 | 1 | 2 | 12 | 3 | 8 | 1 | 24 | 7 | 29 | 15 | 63 | 2 | 8 |
| Scharlach R ointment | 12 | 2 | 9 | 1 | 2 | 12 | 3 | 8 | 1 | 24 | 5 | 21 | 17 | 71 | 2 | 8 |
| Tetrodine powder | 12 | 6 | 4 | 2 | 2 | 12 | 5 | 6 | 1 | 24 | 11 | 45 | 10 | 43 | 3 | 12 |
| Control | 4 | .. | .. | .. | 2 | .. | .. | .. | .. | 20 | | | | | | |

intensity, a striking parallelism was observed in comparison with the previous clean and infected wound experiments. These data are summarized in Table VIII.

TABLE VII

COMPARATIVE RATE OF HEALING OF CLEAN AND INFECTED WOUNDS USING CHLOROPHYLL, VITAMIN OINTMENTS, SULFA COMPOUNDS AND TETRODINE

| Test Agent | Accelerated | | Unaffected | | Delayed | |
|---|---|---|---|---|---|---|
| | Clean | Infected | Clean | Infected | Clean | Infected |
| Chlorophyll preparations | 67.0 | 63.0 | 27.5 | 28.0 | 5.5 | 9.0 |
| Vitamin ointments | 18.4 | 19.4 | 71.6 | 70.8 | 6.0 | 9.7 |
| Sulfa compounds | 3.8 | 27.1 | 45.0 | 57.3 | 51.2 | 15.6 |
| Tetrodine powder | 5.0 | 45.0 | 60.0 | 43.0 | 35.0 | 12.0 |

As in the previous studies, the response in the rate of healing was found to be greater with the various chlorophyll preparations than with any of the other test agents, ranging from 62 to 83 per cent, with an average figure of 71 per cent. There seemed to be no striking relative differences in this rate between the larger (5.0 cm.), more severe burns and the smaller (2.5 cm.) lesions produced at a lower temperature, although obviously the larger lesions took somewhat longer to heal. In this series of animals the Bio-dyne did not seem to be particularly effective in hastening the repair process, although the resultant scar tissue formation was of excellent quality with but little contraction and deformity. The methionine and Scharlach R (amino-azotoluene azobetanaphthol) ointments and the Castilian malva wet dressings showed up a little better in this group of experiments with a slight acceleration of the healing process in from 40 to 50 per cent of the cases. It is our impression that these agents have more effect upon epitheliza-

TABLE VIII

HEALING OF EXPERIMENTALLY INDUCED, DRY HEAT, MILD, THIRD DEGREE BURNS IN DOGS

| Test Agent | 2.5 Cm. | | | | | | | | | 5.0 Cm. | | | | | | | | | | Summary | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 250°C.—20 Seconds | | | 300°C.—30 Seconds | | | | 250°C.—20 Seconds | | | | 300°C.—30 Seconds | | | | | | Healing | | | | | |
| | | | Healing | | | | Healing | | | Healing | | | | Healing | | | | | | | | | | | |
| | No. Animals | No. Lesions | Accelerated | Unaffected | Delayed | No. Lesions | Accelerated | Unaffected | Delayed | No. Lesions | Accelerated | Unaffected | Delayed | No. Lesions | Accelerated | Unaffected | Delayed | Total Number of Lesions Treated | Accelerated | Per Cent | Unaffected | Per Cent | Delayed | Per Cent |
| Chlorophyll—alkaline solution | 4 | 8 | 6 | 2 | 0 | 4 | 2 | 2 | 0 | 8 | 5 | 2 | 1 | 4 | 2 | 2 | 0 | 24 | 15 | 62 | 8 | 33 | 1 | 5 |
| Chlorophyll—lanoline ointment | 4 | 4 | 2 | 1 | 1 | 8 | 5 | 3 | 0 | 4 | 3 | 1 | 0 | 8 | 6 | 1 | 1 | 24 | 16 | 67 | 6 | 25 | 2 | 8 |
| Chlorophyll—jelly | 4 | 4 | 3 | 1 | 0 | 4 | 4 | 0 | 0 | 8 | 6 | 2 | 0 | 8 | 7 | 1 | 0 | 24 | 20 | 83 | 4 | 17 | 0 | 0 |
| Chlorophyll—wet dressing + ointment | 4 | 8 | 6 | 2 | 0 | 8 | 6 | 1 | 1 | 4 | 2 | 1 | 1 | 4 | 2 | 2 | 0 | 24 | 16 | 67 | 6 | 25 | 2 | 8 |
| Chlorophyll—wet dressing + jelly | 4 | 6 | 5 | 1 | 0 | 6 | 4 | 2 | 0 | 6 | 4 | 2 | 0 | 6 | 5 | 1 | 0 | 24 | 18 | 75 | 6 | 25 | 0 | 0 |
| Total chlorophyll | 20 | 30 | 22 | 7 | 1 | 30 | 21 | 8 | 1 | 30 | 20 | 8 | 2 | 30 | 22 | 7 | 1 | 120 | 85 | 71 | 30 | 25 | 5 | 4 |
| Bio-dyne ointment | 4 | 6 | 1 | 4 | 1 | 6 | 2 | 4 | 0 | 6 | 1 | 5 | 0 | 6 | 1 | 3 | 2 | 24 | 5 | 21 | 16 | 67 | 3 | 12 |
| Vitamin B ointment | 2 | 3 | 1 | 2 | 0 | 3 | 0 | 2 | 1 | 3 | 0 | 3 | 0 | 3 | 1 | 2 | 0 | 12 | 2 | 17 | 9 | 75 | 1 | 8 |
| Vitamin C ointment | 2 | 3 | 2 | 1 | 0 | 3 | 1 | 1 | 1 | 3 | 0 | 2 | 1 | 3 | 1 | 2 | 0 | 12 | 4 | 33 | 6 | 50 | 2 | 17 |
| Vitamin D ointment | 2 | 3 | 1 | 1 | 1 | 3 | 2 | 1 | 0 | 3 | 1 | 2 | 0 | 3 | 0 | 2 | 1 | 12 | 4 | 33 | 6 | 50 | 2 | 17 |
| Methionine ointment | 2 | 3 | 2 | 1 | 0 | 3 | 1 | 2 | 0 | 3 | 1 | 1 | 1 | 3 | 2 | 1 | 0 | 12 | 6 | 50 | 5 | 42 | 1 | 8 |
| Castilian malva infusion | 2 | 3 | 1 | 2 | 0 | 3 | 1 | 1 | 1 | 3 | 2 | 1 | 0 | 3 | 1 | 2 | 0 | 12 | 5 | 42 | 6 | 50 | 1 | 8 |
| Sulfanilamide powder | 2 | 3 | 0 | 1 | 2 | 3 | 0 | 2 | 1 | 3 | 0 | 0 | 3 | 3 | 0 | 1 | 2 | 12 | 0 | 0 | 4 | 33 | 8 | 67 |
| Sulfathiazole powder | 2 | 3 | 0 | 2 | 1 | 3 | 0 | 2 | 1 | 3 | 0 | 1 | 2 | 3 | 0 | 2 | 1 | 12 | 0 | 0 | 7 | 58 | 5 | 42 |
| Sulfathiazole ointment | 2 | 3 | 0 | 2 | 1 | 3 | 0 | 1 | 2 | 3 | 1 | 2 | 0 | 3 | 0 | 1 | 2 | 12 | 1 | 8 | 6 | 50 | 5 | 42 |
| Sulfadiazine spray | 2 | 3 | 1 | 1 | 1 | 3 | 0 | 2 | 1 | 3 | 0 | 2 | 1 | 3 | 0 | 1 | 2 | 12 | 1 | 8 | 6 | 50 | 5 | 42 |
| Scharlach R ointment | 2 | 3 | 1 | 2 | 0 | 3 | 2 | 1 | 0 | 3 | 2 | 0 | 1 | 3 | 1 | 2 | 0 | 12 | 6 | 50 | 5 | 42 | 1 | 8 |
| Tetrodine powder | 2 | 3 | 1 | 2 | 0 | 3 | 1 | 1 | 1 | 3 | 0 | 2 | 1 | 3 | 1 | 2 | 0 | 12 | 3 | 25 | 7 | 58 | 2 | 17 |
| Control | 2 | 4 | .. | .. | .. | 4 | .. | .. | .. | 4 | .. | .. | .. | 4 | .. | .. | .. | 16 | | | | | | |

tion than upon the development of healthy granulation tissue as is the case with chlorophyll. Likewise, it should be noted that the actual amount of acceleration with these three agents seldom exceeded two to three days as compared with the 25 to 30 per cent obtained with chlorophyll. In the case of the vitamin preparations, a similar slight acceleration in the healing rate in some of the animals was observed, but this was counterbalanced by a like delay in others so that the net result was of no statistical significance. With the sulfa compounds a very definite delay in healing was found to be the rule, which was even more striking than that noted in the clean surgical wound series. Only in the presence of infection did the sulfa drugs exhibit their real effectiveness, permitting healing to proceed more promptly than in the control lesions through their bacteriostatic action.

TABLE IX
SUMMARY—ALL EXPERIMENTS

| Test Agent | Total Lesions Tested | Accelerated | | Unaffected | | Delayed | |
|---|---|---|---|---|---|---|---|
| | | No. | Per Cent | No. | Per Cent | No. | Per Cent |
| Chlorophyll preparations.. | 448 | 304 | 67.9 | 120 | 26.7 | 24 | 5.4 |
| Vitamin ointments..... | 228 | 40 | 17.5 | 162 | 71.0 | 26 | 11.5 |
| Sulfa compounds..... | 304 | 31 | 10.1 | 144 | 47.4 | 129 | 42.5 |
| Bio-dyne ointment..... | 88 | 26 | 29.5 | 55 | 62.5 | 7 | 8.0 |
| Methionine ointment..... | 76 | 26 | 34.2 | 43 | 56.5 | 7 | 9.3 |
| Castilian Malva infusion..... | 76 | 27 | 35.5 | 43 | 56.5 | 6 | 8.0 |
| Scharlach R ointment..... | 76 | 23 | 30.2 | 43 | 56.5 | 10 | 13.3 |
| Tetrodine powder..... | 76 | 15 | 19.7 | 44 | 57.9 | 17 | 22.4 |
| Totals..... | 1,372 | 492 | 35.8 | 654 | 47.6 | 226 | 16.6 |

In Table IX will be found summarized the results of all three groups of experiments. It will be noted, that, including all three types of experimentally induced lesions in all four test animals, the rate of healing was accelerated appreciably in 67.9 per cent of the animals on which the various chlorophyll preparations were used. This percentage is approximately twice that obtained with any of the other preparations studied and five times as great as that recorded with the various sulfa compounds. In only 6 per cent of the animals on which chlorophyll was used was any delay in healing noted and in the majority of those cases there was secondary infection present not controlled by the drug.

## COMMENTS

An attempt has been made in the foregoing experiments to evaluate the effect of topical application of various agents currently of interest in the treatment of wounds, of both traumatic and thermal origin. A standard procedure has been followed that the results might be critically compared. The method has the advantages of simplicity and uniformity which might make it useful to others working in this same field. By establishing such a standard technic, experimental studies from different laboratories could be more satisfactorily compared or contrasted, data could be easily duplicated for purposes of confirmation, and a universal understanding of each other's reports might hasten the solution of many acute problems in this field.

In these studies the objective has been strictly empirical and factual: to note the length of time required to heal a standard wound. No attempt has been made to theorize or to explain the manner of action of any of the agents under consideration. In earlier papers in this series, it has been shown that chlorophyll has a growth stimulating effect upon fibroblasts in tissue culture, and that it possesses certain bacteriostatic capacities. Its mode of action is still most obscure, but the practical application of these properties, which it has been shown to possess, to wound healing has been substantiated by the data presented in this report. We believe the use of chlorophyll should be extended widely in the clinical field possibly in conjunction with or subsequent to the more actively anti-bacterial agents such as the sulfa drugs. Its use in war injuries and burns

seems particularly indicated at this time in view of the results recorded here.

It has been of great interest to us to learn of the comparative ineffectiveness of any of the vitamins applied locally. While much of the recent work, such as that of Bartlett, Jones and Ryan[3] and Hunt,[17] has emphasized the value of an adequate vitamin C dietary intake in wound healing, its local application as demonstrated in these studies is practically negligible. Slightly more favorable results have been noted by Abramowitz[1] and Hardin[15] with the use of vitamin A and D ointments locally, but we have been unable to confirm this in these experiments. In the use of the sulfa drugs the resultant delay in wound healing is more than offset by their value in controlling infection. Our studies merely tend to confirm other, similar observations in this respect, notably those of Goldberger[13] and Bick.[4] In the clinical field the recent work of Reid,[22,23] Thompson and Ravdin,[26] Koster and Kasman,[18] Allen and Koch,[2] Whipple[28] and Elman[12] lay emphasis on the importance of correcting any existent hypoproteinemia which may exist. This aids in reducing the "lag" period by stimulating normal, healthy cell growth and providing the necessary adequate protein nutritional requirements.

Methionine was employed in this study with the idea of supplying the well established growth stimulating sulfhydryl radical. The results would seem to point to at least a partial utilization of this factor, although nothing very conclusive can be drawn as an inference with such a relatively small number of lesions. Castilian malva has been used in certain parts of the southwest and Mexico, more or less empirically, in various circulatory disturbances of the extremities accompanied by tissue breakdown with what have been claimed to be most encouraging results. It is now under laboratory and clinical investigation to learn something of its effects and pharmacologic action. In our studies, infusions, prepared from the crude, dried leaf have been used both in tissue culture and wound healing experiments. That the drug has some definite pharmacologic activity appears unquestionable, and further investigation into its behavior seems indicated.

In these wound healing experiments Bio-dyne ointment has likewise shown some slight suggestion of accelerating the reparative process. Its antiseptic component has been fairly effective in controlling infection, but again, any beneficial results noted have not been particularly striking. With Tetrodine, it is our impression we are dealing with an agent with all the antiseptic effects of tincture of iodine, but with very few if any of the objectionable features of tincture. It does not appear to delay healing appreciably because of its relatively minimal toxic effect upon tissues, and indeed, healing is definitely hastened in infected wounds as compared with the control animals by overcoming the infection. In this respect, it seems more effective than any of the sulfa compounds studied. Scharlach R ointment appears to be very ineffectual in accelerating the wound healing mechanism. Its much vaunted epithelial stimulating action seems practically negligible in our experience, and this impression has been recorded likewise recently by Boehringer and by Brush and Lam.

## SUMMARY AND CONCLUSIONS

1. The effect upon the healing of 1,372 experimentally induced wounds and burns by the topical application of seventeen medicinal preparations is presented.

2. A control series of 878 similar lesions is included.

3. The agents tested include: Chlorophyll (aqueous soluble derivatives) in five vehicles, vitamin A, vitamin B complex, vitamin C ointments, bio-dyne ointment, methionine ointment, Castilian malva infusion, sulfanilamide powder, sulfathiazole powder and ointment, sulfadiazine spray, Scharlach R ointment, and tetrodine dusting powder.

4. Of all these agents, only the chlorophyll preparations consistently showed any statistically significant effect in ac-

celerating the healing of both traumatic and thermal wounds.

5. Wound healing in 448 lesions in this group was accelerated by 24.9 per cent in time, in 304 or 67.9 per cent of the cases.

6. Vitamin B, C and D ointments showed no appreciable effect.

7. Bio-dyne and methionine ointments and Castilian malva wet dressings (infusion) caused a slight acceleration of healing in somewhat less than a third of the cases, but of less than 10 per cent in time.

8. The sulfa compounds caused definite retardation of the healing process except in the presence of active infection.

9. Scharlach R ointment was essentially inert, acting merely as a protective dressing similar to boric ointment or petrolatum gauze.

10. Tetrodine, an active, stable, aqueous soluble iodine preparation (with an iodine content of 4 per cent combined iodine and 2 per cent free iodine) reduces the healing time in about half the cases when infection is present. In the absence of infection some slight delay in healing is found presumably because of minor tissue irritation.

11. On the basis of these observations it is suggested that chlorophyll preparations should be used much more extensively in the treatment of wounds and burns.

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# IMPLANTATION OF THE URETERS INTO THE LARGE INTESTINE*

## REPORT OF TWO CASES

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THE cloacal condition, which exists normally in fowls and is also the condition which exists during the first weeks of the human embryo, early suggested the thought of making such a deflection of urine through the rectum. Such a method secured a retentive space under control, and was comparatively easy of accomplishment.

In 1790, Petit called attention to the valve-like openings of the ureters, and it is over ninety years since ureterorectal and vesicorectal anastomoses were made by Simon, followed later by Lloyd, and Johnson. The variety of the valve type of operation was also reported by Fowler (1898), Martin, Carl Beck (1899), and later by Frank. Coffey made an extensive investigation concerning the valve function of the duct openings of both the common duct of the liver and of the pancreas. He proved experimentally and mechanically that the valve effect is caused by the extension of the duct for some distance between the mucosa and the muscularis.

Cabot has shown that the ureter is similarly placed in the wall of the bladder for a distance of 1 to 1.5 cm. Direct transplantation of the ureters failed in not providing for compression of the ducts by internal pressure, thus permitting dilatation of the ureters and regurgitation into them. The method of transplanting the base (Maydl) or a greater portion of the bladder (Moyniham, 1906) into the wall of the rectum is practical, as it then becomes subject to the same internal tension as the rest of the intestine. This method is not difficult of accomplishment in the male.

Those operations in which the ureters are transplanted and have been preserved to their tips are correct only in principle if they are made after one of the methods which secures compression of the lumen.

The Coffey operation which Charles Mayo described as practically a divided Martin, is accomplished by separating the ureters that have been isolated and brought through the posterior peritoneum, the distal ends being ligated and buried. A double-needled ligature is attached to the split ends of each ureter. At a point as low as convenient the sigmoid is held in a curved, rubber-covered clamp to protect against the discharge of intestinal contents. The bowel is then incised longitudinally for one and one-quarter inches through the peritoneum and muscularis, but not the mucosa; the mucosa is perforated at the lower end of the incision. The two needles are passed into the lumen of the bowel through the opening and out of its wall, slightly separated, one-half inch lower down, and are used to draw the ureter through the opening into the lumen, where it is held by tying the two threads. The cut muscularis and peritoneum are now closed over the ureter in the incision by two rows of sutures. The second ureter may now be attached or preferably the operation delayed for a later period. The Stiles operation (1907) and that of Mirotworzeff, which method is nearly the same and was reported in 1910, Charles Mayo states secure much

* Read before the Brooklyn Surgical Society, November 13, 1941.

the same effect by infolding the bowel over the ureter by numerous sutures, like a Witzel gastrostomy.*

On November 4, 1897, before the Brooklyn Surgical Society Dr. G. R. Fowler presented a case of extrophy of the bladder in which implantation of the ureters into the rectum, by a new and original method, had been performed at the Brooklyn Hospital, September 20, 1896. The history of the case is as follows:

E. W., aged six, referred by Dr. McCleary, was admitted to the Brooklyn Hospital, with extrophy of the bladder and epispadias. In view of the unsatisfactory results following the plastic procedures designed to restore the defect in the anterior abdominal and bladder walls in this class of cases heretofore in use, it was decided to utilize the rectum, as a receptacle for the urine, which, according to O'Bierne, is practically empty during the intervals of defecation, the feces being stored at the sigmoid flexure.

The abdomen was opened in the median line, with the patient in the Trendelenburg position, the rectum being thoroughly cleansed primarily. The ureters were identified in their relation to the vessels, the posterior layer of the peritoneum incised for a sufficient extent to expose them freely, and the ureters traced to their termination upon the bladder wall, from which they were detached. The ends of the ureters were cut off obliquely.

A longitudinal incision 7 cm. long was made in the anterior wall of the rectum, only the serous and muscular coats being included in the incision. The edges of this incision were retracted, a diamond-shaped space in the submucous space being thus exposed. A tongue-shaped flap of mucous membrane, with its base directed upward, was cut from the mucous membrane of the bowel in the lower half of the diamond. This tongue-shaped flap was doubled upon itself in an upward direction in such a manner that one-half of its mucous surface presented anteriorly, where it was secured by one or two catgut sutures. A flap was thus secured, both sides of which were covered with mucous membrane.

The ureters were now placed in the incision with their obliquely cut ends lying upon the presenting mucous membrane surface of the flap. Two catgut sutures served to secure the ureters in position at this point, and two more were placed in the space represented in the upper half of the diamond, care being taken that these sutures did not invade the lumen of the ureters. The flap-valve and attached ends of the ureters were then pushed into the cavity of the rectum, and the rectal wound closed as follows: The gap in the mucous membrane left by the reflected half of the tongue-shaped flap was first sutured by a running catgut suture. The original wound in the rectal wall was then closed by fine silk sutures, the upper two or three of these being likewise utilized for still further securing the ureters where they passed in the submucous space in the upper half of the diamond. The abdominal wound was then closed.

Prompt recovery followed the operation. The rectum became remarkably tolerant of the presence of urine from the first day following the operation, urination occurring per rectum on an average of every three hours. As time passed this toleration became more pronounced, until at the present time the intervals do not exceed the normal.

The bowel performs without apparent difficulty the double function of a receptacle for both feces and urine. While urination takes place at normal intervals, defecation likewise takes place at normal intervals. The former occurs about once in six hours; the latter takes place but once daily. The movement is generally formed and is not mixed with or accompanied by urine, as far as gross appearances can determine.

Ordinary cleansing after each act of urination suffices to prevent excoriations and eczematous conditions in the anal region, no trace of which is present. The child up to this time, fourteen months after the operation, has shown no evidence of renal disturbance. He attends the public school, and suffers not the slightest inconvenience from the presence of the urine in the rectum.

The following objects are claimed to be obtained by this method of operating:

1. Regurgitation of urine, or passage of feces into the ureters, is prevented by an efficient and permanent valve with a mucous surface applied to the open mouths of the ureters.

* Here and there some of the above is quoted though not verbatim from Charles Mayo.

2. The circular muscular fibers of the bowel wall make compression upon the ureters as they lie in the space beneath the muscular coat of the rectum, thus securing occlusion, and affording additional security against regurgitation during the act of defecation.

The after-course is as follows: This boy grew up to manhood, married, supported himself, and was free from disease or from trouble of any kind for many years. I saw him sometime in 1927 or thereabouts with his physician, Dr. A. Ross Mathewson. He wished to know if his defect in the abdominal wall could be operated upon and corrected. I advised against such an operation.

The next I heard of W, he was a patient in the clinic of the New York Hospital in 1939 and subsequently was admitted to the New York Hospital and was operated upon May 31, 1941.

The following is a copy of a photostat of the summary of the history taken in the New York Hospital.

History No. 225529. This is the first admission of a fifty year old married white male. The chief complaint was various pains and malaise of one week's duration. His family history was negative including deformities. He had had bilateral inguinal hernioplasties fifteen years ago. His general health was good until two years ago when a chronic cough developed. It had become more severe. He was seen in the pulmonary out-patient department where sputum was negative for A.F.B. and the chest plate showed increased markings in the lungs. He lost twenty-five to thirty pounds in the past two years. Occasionally, the cough was so severe that he might vomit. He had frequent colds, his nose was usually much congested with mucous. He was quite short of breath on exercise but could sleep flat.

The patient was born with complete epispadias, a wide open bladder neck, but apparently without complete evagination of the bladder. At the age of six a bilateral uretero-intestinal transplant was done by Dr. G. R. Fowler, of Brooklyn. The operation was described in two articles, one in the American Journal Medical Sciences, March 1898, and on page 313–314 of volume II, "Treatise on Surgery" by Dr. Fowler (Saunders Co.) 1906. The result, at least until two years ago, has been perfect. He had no pyelitis-like attacks, no proctitis and no impotence. He has worked regularly. He is married and has two living children. Sexual relations have always been satisfactory in spite of the deformity. The patient had voided rectally every three to four hours night and day. Occasionally, if sleeping very soundly, he might wet the bed; otherwise he had been able to tell when the rectum was full. His wife stated that he had had frequent dull pains in the region of the kidneys, none of which, however, had interfered with his work until two years ago. Two years ago he was sent to the Urological Clinic and Pulmonary Clinic regarding chronic cough. I-V pyelograms showed a coral stone on the right side, with no evidence of function in two hours. On the left side was a poorly functioning hydronephrotic left kidney. Blood urea nitrogen February 10, 1939, was 40. For the past two years, his general health had been poor. He had lost thirty pounds. He had frequent colds, furuncles, and his cough caused considerable trouble. He had also had dull pain in both kidney regions, particularly on the right. Frequency had increased from three to four hours to one and one-half hours. One week before he developed malaise, vague muscle and joint aches, anorexia, and particularly a bowel frequency, that is, passage of feces with each urination, and desire to pass feces. Ordinarily feces are only passed one to two daily. He had been in bed for the past week and eaten very little. He had no chills or fever.

Physical examination revealed a well developed, somewhat underweight, pale, listless male of fifty-one in no distress, but looking ill, and with a uremic odor to the breath. Examination of the head, eyes, ears, nose, throat and neck showed bilateral nasal obstruction (partial) with considerable mucous. The pharynx was chronically inflamed. The chest was clear and the heart negative. Blood pressure was 85/60. There were bilateral strong inguinal hernia repairs. The symphysis pubis appeared wide. There was a suprapublic vertical scar. The penis was wide without complete urethra. This was completely epispadic with a dorsal groove which opened into the bladder. The bladder neck would admit the index finger. The bladder mucosa was pale pink, and smooth. Tests were unremarkable. Rectally, there were small external tabs. The prostate was enlarged about one-half times, slightly nodular on the right side. It could be palpated bimanually

with one finger in the bladder and one in the rectum. Extremities and reflexes were negative.

Filtered specimen of the urine showed a 4+ albumin, concentration to 1015. No sugar was present. Red and white blood cells were seen. Hemoglobin was 12.5 Gm., red blood cells, 4.1 million; white blood cells, 18,700; and an increase of polymorphonuclears. Serology report was negative in 1939. Blood urea nitrogen on admission was 150; thereafter it varied between 132 and 172.

Fluids were forced, particularly parenterally. His output was over 1,000 cc. daily. His general condition, however, failed to improve. *X*-rays taken showed a coral stone on the right side, and no positive evidence of function on the left side. Accordingly, under local anesthesia a left nephrostomy was carried out. The patient's general condition continued steadily down hill, and following operation his temperature rose to 39.4°C. He became comatose on the first postoperative day. His blood urea nitrogen remained elevated. The patient expired without any striking change, signs or symptoms. Permission for autopsy was obtained.

The body was that of a well developed, moderately obese, white man who appeared slightly older than the stated age of fifty years. The body weighed 69 kilograms and measured 173 cm. in length. There was rigor throughout the body and slight livor over the posterior aspects of the body. The skin of the face and neck showed spots of livid discoloration. The face and neck appeared swollen but no pitting could be elicited. The hair of the head was abundant and gray. The eyebrows were brown. The eyelids were slightly swollen, the right more than the left; this was probably due to edema. There was a small pedunculated papilloma in the outer upper corner of the left eyelid. The eyeballs were moderately protruding. The corneae showed beginning drying. The right pupil was slightly larger than the left, measuring 3.5 mm., the left 3 mm. The right pupil appeared slightly gray, the left black. The conjunctivae were pale. There was a small amount of purulent discharge in the right conjunctiva. There was also purulent discharge in the nostrils. The oral cavity could not be examined because of rigor. Several teeth were absent, others were carious. About the right lower lateral teeth the margin of the gum was red and covered with necrotic material. The lymph nodes of the neck were not palpable. The skin of the neck was covered with white, dry powdery material (uremic snow?). There was a well healed left rectus incision measuring 6 cm. in length and another well healed surgical incision extended from beneath the umbilicus to the symphysis pubis measuring 7 cm. in length. There was a healed surgical incision above the right iliac crest measuring 12 cm. in length. There was a fistulous opening at the symphysis pubis which entered the region of the bladder. The upper margin of this fistulous opening was marked by a stellate scar. There was a left transverse incision above the kidney extending from the midscapular line to the midclavicular line. This incision was very recent; it had been sutured by black silk and drained by two rubber tubings. There were several needle puncture wounds in the antecubital fossa. The extremities appeared slightly swollen but showed no pitting on pressure.

The usual incisions were made for examination of the chest and abdomen. The contents of the cranium were exposed by an intermastoidal incision.

The peritoneal cavity contained no measurable amount of fluid. The serosal surfaces were smooth and shiny and the relationship of the organs was normal. There were few fibrous adhesions between the appendix and the peritoneum. The appendix was curled up and lay behind the cecum. The pleural cavities contained about 15 cc. of clear serous fluid and the serosal surfaces were smooth and shiny.

The heart weighed 300 Gm. This organ was of normal size and shape. The valvular orifices measured as follows: tricuspid valve 13.5 cm.; mitral valve, 11 cm.; aortic valve 7.5 cm.; pulmonic valve, 8 cm. The myocardium of the left ventricle measured 16 mm. in thickness, that of the right ventricle 4 mm. The chambers were of normal dimensions. The valve leaflets were all smooth and delicate, save for the presence of an atheromatous plaque measuring approximately 1 cm. in greatest diameter in the aortic leaflet of the mitral valve. The foramen ovale was closed. The branches of the coronary artery showed slight sclerosis. The lumen of the vessel was not harrowed at any place. The thoracic aorta showed slight sclerosis; the abdominal aorta was moderately sclerosed. Calcified patches were very few and the degree of calcification scant. Ulceration was absent. The orifice of the right renal artery was very small, measuring only 3 mm. across

(about one-half that of the left). There was slight sclerosis of the base of the aortic leaflet.

The two lungs together weighed 1,800 Gm. This increase in weight of the lungs was due entirely to intense congestion and edema. The bronchi were red and the bronchial tree was filled with a moderate amount of red-tinged mucous exudate. There was a fibrous scar in the posterior part of the apex of the right upper lobe, measuring 3 by 2.5 cm. on the pleural surface. This scar did not effect the underlying lung tissue. No apical scar was noted in the left pleura and calcified nodes were not identified in the lung or in the tracheobronchial lymph nodes. There was moderate anthracosis of the tracheobronchial lymph nodes which were slightly to moderately enlarged. The largest of these measured approximately 2.5 by 2 by 1.5 cm. Several of these anthracotic nodes were soft and one such node was sectioned. A gray-white, firm tumor node measuring 4 by 4 by 2 mm. was found in the mucosa of the left main bronchus close to its bifurcation.

The liver weighed 1,800 Gm. The organ was brown-red, of the usual consistency. It was of normal shape and of approximately normal size. The gallbladder and billiary tract showed no change. The esophagus was normal. There were a few small erosions at the junction of the esophagus with the stomach. The stomach itself presented no change. The mucosa was covered with a moderate amount of tenacious mucus. The small intestine showed no change. The large intestine was also normal. There was great distention of the cecum and rectum. The content of the large intestine was green and soft, in part fluid.

The appendix measured 10 cm. in length. Fibrous peri-appendiceal adhesions have already been mentioned. There were numerous petechiae in the sigmoid colon. The spleen weighed 250 Gm. As the weight indicates the organ was slightly enlarged. The capsule was normal, the follicles distinct and of normal size. The trabecular network could not be defined. The pulp was very soft and a large amount of red pulp material could be readily scraped from the cut surface of the organ. The pancreas measured 23 by 4.5 by 2.5 cm. The organ showed no gross change. The adrenals were of normal size, shape and consistency. The cortex was yellow, the medulla gray.

The right kidney measured 6 by 4 cm. in the two greatest diameters. This organ, as the size indicates, was very small. It was embedded in a large amount of fatty tissue. The capsule could not be identified, neither could cortex and medulla be defined. The organ consisted of gray-white tissue with numerous minute cavities containing yellowish, turbid material. The right ureter entered the sigmoid-rectal junction 20 cm. above the anal orifice. The right ureter measured approximately 15 mm. in diameter, or approximately 2.5 cm. in circumference. The wall of this ureter was greatly thickened, the greatest thickness measuring approximately 3 mm. This ureter was filled with purulent material. Its orifice at first could not be probed. Further tests, however, showed it to be permeable to water and subsequently a fine probe could be passed through it. The renal pelvis on this side was contracted and filled with a stone which followed the ramification of the calices. Around this stone a large amount of turbid fluid was found.

The left kidney measured 11 by 7 by 4 cm. The left ureter was wider than the right measuring in circumference 4.5 cm. However, the wall of this ureter was not as thick as the right and measured only 2 mm. This ureter in contrast to the right was very tortuous so that it could not be readily probed. The tortuosity was greatest at the pelvic-ureteral junction. The kinking here was so great that it is possible that this contributed to the development of the hydronephrosis. There was also some kinking in the region of the junction of this ureter with the sigmoid colon. This kidney contained no stones. However, there was an incision wound on the lateral aspect of the organ with a catheter lying in and draining the lower calyx of the renal pelvis. This pelvis was dilated. No frank purulent material was identified in this renal pelvis and the content of this ureter was turbid yellowish material similar to that in the right kidney. The ureters were not opened until after fixation of the organ. There was a hemorrhage in the left renal capsule. This kidney, in contrast to the right, was sharply outlined and was free from perirenal adhesions and perirenal inflammation. Two rubber tubes, in addition to the one already mentioned, drained the peripelvic region. The two ureters entered the rectum close to each other. A depression in the mucosa of the rectum measuring 6 mm. across beneath their entry marked this site.

Three vertebrae were cut across. The bone marrow was of normal red color. The bony

meshwork was as usual, or perhaps slightly wider than usual and the bones were of normal consistency, if not slightly softer than normal.

There was a complete epispadias. The bladder was small, measuring approximately 3 by 3.5 cm. in the two greatest diameters. The prostate and seminal vesicles showed no change. Testes and epididymides were free from abnormalities.*

The following case of unilateral implantation presents some interesting observations:

E. V., a male, age thirty-one, was first seen by the author on April 6, 1940. A diagnosis of intractable fistula of the left ureter with stone embedded in lower end of ureter and with deep abscess was made on the examination and history. He was referred to the Wyckoff Heights Hospital for further observation and operation. It was explained to him that an attempt would be made to restore his ureter and that if this was found impossible the ureter would be implanted into the bowel and an attempt also made to remove the stone. It was explained to him that this method of treatment was advised rather than nephrectomy even though the kidney might prove to be infected and a nephrectomy later be necessary.

For the past four years, the patient had several attacks of pain beginning in the back and radiating to the front of the abdomen. The pain was severe and accompanied by vomiting. During the week of September 25, 1939, he was cystoscoped at Coney Island Hospital and a diagnosis of stone made for which he was operated upon during the week of January 1, 1940. He was subsequently told that it was impossible to remove the stone and that it was pushed down into the bladder during which process the ureter was damaged. A few days later an infection occurred following which the wound healed slowly and a fistula persisted from which urine has been draining ever since. In the latter part of April, 1940, he began running a temperature of 101° to 105°F. —normal during the day and elevated at night. A few days later pus began draining from the sinus as well as urine.

Physical examination revealed a well developed, white male, not appearing acutely ill. Physical examination was negative except for the urinary fistula.

He was cystoscoped on April 7, 1940, by Doctor Mule. There was cloudy bladder urine and a moderately congested trigone. A No. 5 catheter passed easily to the right pelvis and cloudy urine obtained. A filiform could be passed only 1 cm. up the left ureter. No urine could be obtained from the left ureter. A flat plate and intravenous plates were taken. A retrograde pyelogram of the left ureter was attempted but no dye could be forced up the ureter. Diagnosis: Left ureteral calculus; left hydro-ureter and hydronephrosis.

On April 9, 1940, pus was still draining and his temperature was still elevated so the fistulous tract which extended to the depth of about three inches was dilated with an artery clamp and a No. 14 French catheter inserted through the tract.

Four days later the temperature became normal. Dakin's fluid was dropped into the catheter several times daily and as the catheter became displaced it was re-inserted.

On April 28, 1940, nineteen days after the dilatation of the fistula, the temperature remained practically normal. A left rectus incision was made and the abdomen opened. The peritoneum overlying the ureter was incised and a probe was inserted into the fistula. The fistulous tract was dissected down to the ureter. The lower end of the ureter near the bladder was found to be connected by dense scar tissue. The lower end of the fistulous tract near the ureter was found much enlarged. The proximal end of the ureter was separated from the scar tissue. The scar tissue was incised near the bladder and a small stone removed. The incision for the removal of the stone was closed and covered with peritoneum after removal of some of the scar tissue. The ureter was separated from the scar tissue. It was found impossible to embed it in the bladder. The lower sigmoid was mobilized and the ureter implanted in the lower sigmoid just above the rectosigmoid juncture. This was effected by the Fowler technic, i.e., oblique section of the opened end of the ureter; application of this by fine sutures to the mucous flap with the opening of the ureter against the mucous mem-

* I am much indebted to Dr. George W. Wheeler, Superintendent and Dr. V. F. Marshall, and Dr. John B. Pastore, Assistant Superintendents of the New York Hospital, as well as to Dr. Walter C. Klotz, Director, and Dr. H. J. Truax of the Out-Patient Department, for their generous help in furnishing the New York Hospital records of Walsh.

brane; the laying of the ureter on submucosa above the flap and securing it there with fine sutures. The peritoneal and muscular coats were then sutured over the ureter. No drainage was used in relation to the ureteral implantation but three cigarette drains and a rubber tissue drain were used to drain the pelvis on the left side where there had been much dissection and manipulation. The operation was necessarily a long one taking over two hours. The abdominal wound was closed without drainage; the drains emerged from the excised opening of the fistulous tract. The after course was uneventful. The sutures and all drains were removed on the sixth day and the patient was discharged on the thirteenth day with a healed wound and much improved. There was immediate control of rectal urination and defecation, urination occurring about every six hours per rectum and bowel movements twice daily.

From May 11 to May 24, 1940, there were five office dressings for a small superficial granulating area which had been scabbed over. The wound has remained completely healed since. For the next month there was slight pain occasionally in the left kidney region. The bladder and rectum functioned well. He gained steadily in weight and on January 1, 1941 weighed 179 pounds, a gain of 37 pounds.

On November 13, 1941 he reported that he worked all day and had no pain. He has gained more weight, passes water from rectum four times a day separately from two to three bowel movements; he has to get up occasionally at night when a good deal of fluid has been taken but he has complete control.

He does not find it necessary to pass urine by rectum at the same time that he passes urine by urethra. The controls are entirely independent. This is rather interesting. I have asked him to measure the amount of fluid which he passes by rectum and also the amount of urine which he passes by urethra. He states that the amount of urine by urethra in twenty-four hours is 32 ounces, that the amount of urine per rectum separate from the bowel movements is approximately 32 ounces.

Intravenous pyelogram on October 27, 1941, and plates taken May 15, 1942, at five, fifteen and twenty-five minute intervals showed good function in both kidneys and a normal right urinary tract. The left tract showed a moderate dilatation of the ureter and pelvis, without evidence of obstructive lesion, kinking or otherwise. The left half of the bladder showed a deformity.

G. R. Fowler's next published contribution on implantation of the ureter into the rectum in exstrophy of the bladder was in the American Journal of the Medical Sciences, March 1898, in which he called attention to the unsatisfactory character of the results following operations designed for the restoration of the anterior bladder wall in exstrophy, such as introduced by Dr. Daniel Ayers and the further closure of the accompanying gap in the symphysis after the manner of Trendelenburg.

Konig and Kuster modified Trendelenburg's procedure by substituting osteotomy of the anterior pelvic ring for forced separation of the sacro-iliac junction. All of these procedures are difficult of execution.

Passavant proposed to accomplish closure of the pelvic bony gap by force brisement. C. T. A. Koch, of Growigen (Netherlands), carried out Passavant's proposition in a child of six years and six weeks later closed the defect in the soft parts by suture, reporting the case one week following the second operation.

In 1897, Tietze, of Mikulics Clinic, advised that all attempts to close the bony defect be abandoned and advocated closure by lateral flaps.

Even when exstrophy and the accompanying epispadias were corrected the patient's condition was not greatly improved. Attempts to restore the muscular apparatus of the vesical neck proved unsatisfactory, incontinence persisted, necessitating the wearing of an apparatus difficult to adjust and keep clean.

For these reasons Maydl, in Prag, in 1896, suggested implantation of the ureters into the rectum. This did not meet with marked favor on account of the probability of renal infection. That this fear was not theoretical was proved by clinical experience as well as by the experimented work on animals by Gluck and Zeller, Bardenheuer, Tuffier, Smith and others. These

clinical and laboratory results led to attempts to improve the technique of implantation to prevent renal infection through the open ends of the ureter in the rectum.

Four operative procedures were presented: The first, that of Maydl, had as its basic principle utilizing nature's arrangement of the *oblique* course of the ureter in the bladder wall and the arrangement of the mucous membrane at the vesical opening of the ureter, so Maydl transplanted the bas fond and ureters into the rectum.

Second, Krynski, operated according to the Maydl method on a twenty-three year old man with ectopia vesicae with an excellent result eight months postoperatively. Subsequent to this, in 1896, using dogs, he implanted the ureters into the *submucous connective tissue* space of the rectum by turning back a triangular flap of rectal wall in a lateral direction down to the mucous membrane, implanting the ureters there and making a small opening in the mucous membrane for the passage of urine, then suturing the triangular flap back in place. Krynski's operation is very ingenious and deserves a full description. He operated upon dogs. He never did the operation on man. He did not observe inflammation of the ureter or kidney to follow. His method is illustrated by three line drawings. A triangular incision is made through serosa and muscularis, reflecting the flap thus outlined, and then making an opening through the mucous membrane near the lower point of the triangle, and securing with four sutures the cut ureter with the intestinal wall in the opening, mucous membrane to mucous membrane, finally covering the implanted ureter with the reflected serosa-muscularis triangle and sewing the same in place, the long side with a continuous suture, the short side with individual sutures, two in the intestinal wall and two in intestinal wall and ureteral wall. The ureter is still further secured by suturing it with several interrupted stitches to the intestinal wall. Krynski advises not to sew the reflected flap too tightly over the ureter to avoid constriction of its lumen.

Third, Vignoni, in 1895, on the basis of animal experimentation recommended a v-shaped flap cut from the anterior rectal wall, suturing the ureters upon this and covering them by suturing over them two lateral folds of the bowel wall.

Fourth, Pisani, operating on two dogs in 1895, transplanted part of the bladder wall with the ureter to the *posterior* wall of the rectum by an incision through the anterior rectal wall, removing a portion of the rectal mucous membrane from the posterior rectal wall and suturing the transplanted bladder wall and ureters to this freshened area. The remainder of the bladder was excised. One dog died of shock in sixty-two hours, the other of peritonitis after six days.

Fifth, G. R. Fowler, September 20, 1896, used the operative technic which was described at the beginning of this presentation and which was an original method.

The advantages claimed for this method of operating are as follows:

"1. An efficient permanent valve, with a mucous surface applied to the open mouths of the ureters, is provided. This valve is so situated that it is closely applied to and occludes the open ends of the ureters as the rectum becomes filled with urine, or when fecal matter descends from above.

"2. *Placing the ureters in the submucous space of the rectal wall for a distance of three or more centimeters above the point where these enter the cavity of the rectum affords an additional safeguard against renal infection.* In this situation the circular muscular fibres of the bowel wall compress the ureters and secure occlusion at this point during the act of defecation."

We next find G. R. Fowler's case referred to in his "Treatise on Surgery" in 1906. Unfortunately, the illustrations were not copied correctly from the originals appearing in the American Journal of the Medical

Sciences in 1898, the difference being that the dotted line showing the mucous membrane flap extends into the upper half of the diamond shape area whereas the flap in the original illustration is entirely in the lower half.

G. R. Fowler also failed to include the important observation made in the original report, "*Placing the ureters in the submucous space for a distance of three or more centimeters above the point where these enter the cavity of the rectum affords an additional safeguard against renal infection.*" I call attention particularly to this observation.

Probably the most complete study of transplantation of the ureters into the large intestine was made by Robert C. Coffee of Portland, Oregon.

Many of Coffee's articles later appeared, approximately fifteen in number, through the years 1929 to 1933 in various magazines. W. J. Mayo, in 1908, advised Coffee to take up the study of problems connected with pancreatic surgery. His dissection of the entrance of the common duct into the duodenum and the knowledge acquired in this manner caused him later to apply similar principles to transplantation of the ureters into the large intestine. He reviewed approximately 250 articles dealing with experimental attempts, and states that up to 1909 not one author had constructed a tru-non motile valve such as exists in ordinary mechanics or in the cardiovascular system at the mouth of the ureters or at the mouth of the bile duct.

The first operation cited by Coffee is that of Dr. G. R. Fowler, but unfortunately Coffee apparently got his information in regard to the Fowler operation through Fowler's "Treatise on Surgery" from which he quotes and reproduces illustrations. Had he gone further back to Fowler's original article in the American Journal of the Medical Sciences, he would have found that the original illustrations showed more clearly what the operation was and that Fowler's operation did include the very principle which Coffee advocated as the underlying principle of successful ureteral implantation. Nor does Coffee describe the original procedures of Madyl, Krynski, Vignoni and Pisani.

Coffee gives deserved credit to Franklin H. Martin and shows very beautiful illustrations of the Martin operation. He also describes the Peter's operation. The history of his own procedure and the method of its performance is well described.

Briefly, these three operations, Coffee's, Martin's and Peter's are as follows:

*Coffee's operation* as done by Charles Mayo has already been described. As done by Coffee it is much more complicated and includes elements which are undesirable as inflicting too much injury on the ureter and so interfering with its physiological action.

John William Draper and William F. Braasch who writing on the "Function of the Ureterovesical Valve," stated that

"With few exceptions, all efforts to utilize the septic bowel as a urinary reservoir have signally failed. Has this been because of the destruction of the uretero-vesical valve alone? This has been the general opinion in the past. Has not the physiologic element in connection with this problem been overlooked? If it be true that nature has provided an abundant 'factor of safety' in combining both physiologic and mechanic factors in protecting against reflux, then it may be that the failure to make a vicarious bladder out of the bowel has been due to the destruction of the mechanic protection, coupled with such serious impairment of the physiologic defense as entirely to overbalance the 'factor of safety.' Such physiologic impairment may well be accomplished by the injury to the ureter consequent to its transplantation. Dudley Tait may be quoted as saying that the explanation of the recent occasional success of the ureteral rectal implantation should be attributed to the careful protection of the ureter from traumatism by the modern technic. This has been accom-

plished by discontinuing the use of a permanent catheter after transplantation and by minimizing the number of stitches taken in the ureter. This is directly in line with the idea that reflux is prevented much more by the ureter itself than by the obliquity of its valve. Tait also holds that the importance of the mechanic action of the valve in preventing reflux has been exaggerated.

"This consideration calls to mind the history of the patients in whom a mechanically corresponding valve, that situated at the papilla of Vater, was slit in the transduodenal operation of McBurney for the removal of gall-stones. This operation was done many times and, so far as is known, without grave injury to the patient by reason of reflux of duodenal contents into the common bile-duct, liver, or pancreas. It would appear, therefore, that the destruction of this mechanic safeguard must have placed the work of preventing such reflux on the physiologic function of the duct. This implies that the 'factor of safety' regarding the prevention of reflux into the liver as well as into the kidneys is in each case a double one, formed by a combination of a mechanic valve and a physiologic contrivance.

"Physiologists and anatomists alike, while universally drawing attention to the fact that the mechanic arrangements for the valve are such as to protect the ureter from the transmission of intravesical pressure, do not state that this is its solitary function nor do they summarize the conditions which would be obtained if the valve were destroyed. Here we are on the borderland between surgery and physiology and evidently at a point where the first cannot safely advance except through the help of the second. Have we not, in considering the ureteral valve as the paramount protector of the ureters and kidneys from dangers arising from below, been somewhat biased because of having reasoned from a morphologic point of view alone? Have not the underlying principles of physiology and chemistry been overshadowed and forgotten in the tacit acceptance of this purely morphologic explanation? Indeed, it appears to us that the well-known difficulty of reproducing in animals the analogues of human disease, even though all the evident morphologic and physical conditions be duplicated, should suffice to show us that in the discussion of this as well as of other surgical problems, in considering form alone surgeons have as yet taken only the first primitive step. Were we to attempt to reproduce the ordinary symptoms of human disease in healthy human beings we should without doubt be confronted with the same difficulties that are encountered in making these attempts on animals.

"With these considerations in mind, and believing that the existing surgical studies of the ureteral meatus had been too closely on morphology, since the delicate physiologic regulation both as regards protection from ascending infection, if indeed any such process is possible, and as regards the maintenance of normal glomerulotubular pressure, had all been lost sight of, we made efforts to consider the bearing of these points in our experimental work. We did not expect to answer these questions by any single experimental study, but we hoped to make the subject somewhat clearer and to direct attention to the importance of physiology to applied surgery. We slit the valve in dogs in the belief that the ureter was much more than a mere aqueduct for the conduction of urine, and that the generally recognized check-valve action at the meatus was of contributory rather than of paramount importance. We have been led to believe as a result of these studies that, provided the physiologic and chemic balance of the organism and of the ureter were left intact, the importance of the mechanical action of the valve was correspondingly diminished and that its loss would usually be compensated for by the ureter. These ideas are not original, being simply the natural outcome of an application of mod-

ern physiology to the study of surgical problems.

"Cathelin's views as to the valvular function are pointed. In a paper on the mechanism of the ureteral ejaculation, Cathelin says that the meatus does not open after the manner of a sphincter—that there is not the least suggestion of force or contraction. He regards the opening of the valve as purely passive in character, likening it to the opening and closing of the mouth of a fish."

I cite the above to show the importance of correlating physiology as based on physics and chemistry as well as anatomy in the study of surgical problems such as the one under present consideration.

*Martin Operation.* The intestine is split down to the muscular coat, a stab wound made through the muscular coat and mucosa near the lower angle, the two ureters being drawn into the lumen of the intestine. Ureters are anchored to the inside of the intestine by suture; muscle wall is enfolded around the ureter. Muscular wall is made to envelop ureters for most of the length of the wound, peritoneum being closed over other sutures. The completed operation shows the ureters surrounded by muscle wall.

*Peter's Operation.* This consists of the transplantation of ureters into the rectum by the extraperitoneal method. The ureter is transplanted with rosette of bladder mucous membrane and muscle; the catheter is stitched into the ureter and protruded through the anus.

The indications for implantation of the ureter in the intestine are: (1) Incurable carcinoma of the bladder, urethra, or prostate for palliative purposes; (2) advanced carcinoma of the bladder, urethra, or prostate in which it is impossible surgically to remove the growth, but in which it is possible with the use of large and even ruthless doses of radium to destroy the growth; (3) early curable carcinoma as an essential part of the operation of total cystectomy, which may include prostatectomy in the male or hysterectomy in the female; (4) carcinoma involving the urethra; (5) incurable vesicovaginal fistula; (6) contracted bladder due to scars of ulceration or to other causes; (7) extensive, incurable, multiple perineal fistulas resulting from various causes; (8) tuberculous ulceration of the bladder in which one kidney remains good and the other is to be removed; (9) traumatic injuries which make the use of the bladder impracticable, and (10) exstrophy of the bladder. And to these we add intractable ureteral fistula in which destruction of the ureter is so extensive as to make plastic restoration or bladder implantation impracticable.

## CONCLUSIONS

Any method of implantation to be functionally successful must: (1) Place the ureter in the intestinal wall in the submucous connective tissue for a sufficient distance for it to be compressed in its course there by intra-intestinal pressure while the bowel is acting. (2) Inflict the minimum amount of traumatism to the ureter in the operative procedure to prevent physiologic impairment. (Use few and fine sutures, avoid compression, expose the ureter as little as possible, be gentle.) (3) Avoid kinking to prevent undue obstruction. (4) Cut the ureter obliquely to avoid undue contraction which occurs when any transverse section is made in any tissue. (5) Face the ureters to mucous membrane to minimize forcing of fecal material into them.

G. R. Fowler's operation embodied all of the factors except kinking which in some cases is unavoidable if the more important factor of inflicting the minimum amount of traumatism is strictly observed.

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PROPHYLAXIS requires a thorough debridement of all compound fractures, including radical wound excision when there is extensive laceration or contusion of the tissues. Every puncture wound should be decidedly enlarged. Such treatment has greatly reduced the incidence of gas infection.

# KNEE JOINT ARTHROTOMY IN MILITARY LIFE

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FIFTY arthrotomies of the knee joint were done during a six and one-half month period at the Station Hospital, New Orleans, Louisiana. This communication consists of a study of these cases. Follow-up and end result studies are not feasible in military life, so our observations have been confined for the most part to the periods of hospitalization of these men.

The majority of these arthrotomies were done because of medial meniscus pathology. Brantigan and Voshell[1] have pointed out that the menisci fill an otherwise dead space between the periphery of the condyles of the tibia and femur, and keep the capsule and synovia from becoming pinched between the femoral and tibial condyles. The medial meniscus is more often injured than the lateral, as it is more vulnerable to traumatizing forces which ordinarily affect a knee. The usual type of injury which traumatizes the medial meniscus consists of a sudden forceful abduction and external rotation of the leg on the thigh with the knee in partial flexion. Our patients experienced this by marching on uneven ground, doing about-faces, jumping over obstacle course hurdles, doing knee-bend calisthenics, falling down barracks steps, falling off trucks, crossing muddy streams, and playing football, baseball, and basketball.

Our operative preparation and technic was the same for all fifty cases. The entire extremity is shaved, washed with green soap and water, ether, 70 per cent alcohol, and wrapped in sterile towels twenty-four hours before operation. Spinal anesthesia (100 to 150 mg. novocain) is the anesthesia used. The leg is elevated for three minutes and an Esmarch tourniquet is applied. The extremity, from groin to toes, is painted with ether and then 3½ per cent iodine. Sterile draping is facilitated by the use of a sterile stockinette, and a sandbag is placed under the thigh. A four or five inch vertical parapatellar incision one inch medial, or lateral, to the patellar border is made so that the joint line is at the level of the junction of its upper three-fourths and lower one-fourth. This proved to afford an adequate exposure of the joint. In two cases, through this single skin incision, a second vertical incision was made in the capsule posterior to the medial collateral ligament in order to remove the posterior portion of the medial meniscus. In one case the upper and lower ends of the incision were extended in a curved manner, thus converting it into the so-called utility incision. We condemn small incisions which do not give adequate exposure, since the entire joint should be thoroughly inspected. The infrapatellar branch of the saphenous nerve should be located and protected in order to prevent the annoying hypesthesia below the patella which follows its section. The capsule is incised vertically, but curving along the inner border of the muscle fibers of the vastus medialis (or lateralis) in order not to divide them. The capsule is divided vertically, and the interior of the joint is well exposed. If the medial meniscus is to be excised, a second sterile assistant standing caudad to the operator abducts and externally rotates the lower leg, and slightly flexes the knee. In case the knee is being approached from its lateral aspect, the leg is adducted and internally rotated, and the knee is slightly flexed. The anterior half of the meniscus can be freed with a Bard-Parker type knife. For freeing the posterior half, we use a knife with a long narrow blade (two and one-half inches long

and one-eighth inch in width). These knives were made by simply grinding down ordinary dissecting scalpels. We believe that it is important to remove the meniscus in its entirety, and are not satisfied with excising just the anterior two-thirds or three-fourths. Two of our patients had previously had medial meniscectomies, but were not relieved of their symptoms. In both cases, the posterior portion of the meniscus was found to be present and was removed. Both original meniscectomies had been done through inadequately small incisions. Before closure, a fresh glove is slipped on and the anterior compartment of the knee, including the suprapatellar pouch and undersurface of the patella, is carefully palpated and inspected. The wound is closed in layers using continuous plain catgut for the synovia, continuous chromic catgut for the capsule, continuous plain catgut for the superficial fascia, and continuous silk for the skin.

If the signs and symptoms in a given case have warranted arthrotomy, and upon opening the joint the visible anterior portion of the meniscus appears normal, it is advisable to do a meniscectomy; otherwise tears or other lesions of the posterior portion will be overlooked in many cases. The day after operation, the circular gauze bandage is split vertically on the side opposite the wound in order to avoid any constriction, and an elastic roller bandage is applied over the split gauze bandage without disturbing the dressing. Assisted active motion of the knee, and quadriceps setting exercises for five minutes every hour, are begun at once. On the third or fourth day following operation, the patient sits up over the side of the bed in order to extend and flex his knee actively. One week following operation he becomes ambulatory without the aid of cane or crutches, and baking, massage, and active exercises daily are instituted. The use of a stationary bicycle machine, and extending the leg with the ankle strapped to a weighted rope and pulley apparatus has greatly facilitated the return of quadriceps power.

During the six and one-half month period from August 24, 1942, to March 10, 1943, fifty arthrotomies of the knee were done. The youngest patient was twenty years of age, the oldest was forty-two, and the average age for the group was twenty-five. Thirty-three were in the second decade of life, thirteen were in the third decade, and four were in the fourth decade. Thirty-nine patients were white and eleven were colored, a ratio of 3:5 to 1. Forty-three meniscectomies were done; thirty-eight of these were medial meniscectomies, and five were lateral meniscectomies. Loose (osteocartilaginous) bodies were removed from five knees. Loosened, fibrillated articular cartilage was removed from the medial and lateral femoral condyles and patella in one knee, and in one instance a hypertrophied infrapatellar fat pad and regenerated connective tissue at the site of previous meniscectomies were excised.

Of the thirty-eight medial meniscectomies, twenty-one were done for well defined tears of the medial meniscus. These twenty-one were as follows:

| | Cases |
|---|---|
| "Bucket handle" tear | 8 |
| Longitudinal tear of anterior ⅓ | 1 |
| Longitudinal tear of middle ⅓ | 1 |
| Longitudinal tear of posterior ⅓ | 5 |
| Oblique tear of anterior ⅓ | 3 |
| Oblique tear of middle ⅓ | 2 |
| Oblique tear of posterior ⅓ | 0 |
| Transverse tear of middle ⅓ | 1 |

Seventeen medial meniscectomies were done because of some type of disorder other than a tear. Two were discoid in their posterior halves. Two were the remaining posterior portions not removed at a previous arthrotomy through inadequately small incisions. In seven instances, there was a depression in the articular cartilage of the medial femoral condyle corresponding to the anterior portion of the medial meniscus with the knee in complete extension, and a pannus formation of the medial femoral epicondyle at this point.[2] One presented a

tear of the posterior half of the coronary ligament with displacement of its posterior end into the intercondylar notch. One presented a tear of the entire coronary ligament except at its anterior and posterior ends, and was found lying in an upside-down position. Three were hypermobile; the first was accompanied by fibrillation of the articular cartilage of the medial femoral and tibial condyles and patella, the second presented a bony spurring of the medial femoral epicondyle which was excised, and the third exhibited a small transverse tear of the middle one-third which may have been done in removal. One was accompanied by a cyst of the sartorius, gracilis, and semitendinosis tendon sheaths.

The anterior cruciate ligament was completely avulsed in the knee with the transverse tear of the middle one-third of the medial meniscus. This tear extended half the width of the meniscus, and was not inflicted during the meniscectomy. This patient had sustained a severe injury when "clipped" from the side while playing football. The synovial fluid was grossly bloody and increased in amount. The osteocartilaginous loose bodies varied in size, the largest being one inch by three-fourths inch by one-half inch in size. This particular loose body was removed from the posterior compartment of the knee through a midline posterior incision. One medial meniscus, which presented an oblique tear of its anterior one-third was markedly degenerated, and about one-third its normal width. Numerous small bits of cartilage, apparently arising from the degenerated meniscus, were floating free in the synovial fluid.

Forty-seven of the fifty patients gave a history of injury which was associated with the knee disability. In fifteen instances, this had occurred prior to entry into military service, but these men were unable satisfactorily to continue with their drilling, marching, and calisthenics. In twelve instances, there had been a previous injury in civilian life, followed by another injury in military life. In twenty instances, the initial injury was sustained while in the service. Thirty-four patients gave a history of a single injury, while sixteen gave a history of two or more injuries. All patients, with but two exceptions, who had medial or lateral meniscus disturbance localized their pain to the inner or outer aspect of the knee. The five patients with loose bodies noted diffuse, rather than localized, discomfort or pain. The commonest symptoms complained of were instability of the knee or uneven ground or stairs, actual giving way, temporary locking in partial flexion, swelling, and "snapping" or "clicking" upon flexion and extension. The commonest signs elicited were tenderness over the joint line (in cases of meniscus disorder), effusion, varying degrees of limitation of extension and flexion, and muscle spasm at the extremes of motion. Knees with medial meniscus lesions usually presented pain about the medial aspect of the joint upon forced extension, adduction, and external tibial torsion. The five knees with lateral meniscus lesions (all cysts in this series) presented pain about the lateral aspect of the joint upon abduction and internal tibial torsion, as well as discomfort upon the extremes of extension and flexion. Three of the five cysts of the lateral meniscus were large enough to palpate prior to operation. Atrophy of the calf was noted in some cases of longer duration. Anteroposterior relaxation was evident in the knee with the avulsed anterior cruciate ligament. Palpable loose bodies, which would disappear into the interior of the joint upon flexion and extension, were noted in two cases.

Fifty-one incisions were made in the fifty knees. Forty-seven wounds healed per primam, two wound edges separated and healed by secondary intention, and one became infected. The offending organism in this case was Staphylococcus albus; this occurred in the second patient operated upon, and it is believed that this was an air-borne infection, although this of course cannot be proved. Thirty-three men have returned to duty, while seventeen are still in the hospital. The average period of

hospitalization of the thirty-three who have returned to duty was 40.3 days. The shortest period of hospital stay was seventeen days, and the longest was seventy-two days. Seven men were recommended for reclassification for limited service, and a furlough was recommended for three men.

The findings at operation were of particular interest in five patients. These will be briefly described.

Case I. J. W. T. This thirty-one-year-old white soldier, who sustained a tear of his right medial meniscus in June, 1942, underwent a right medial meniscectomy in July, 1942, before being transferred to this Command Area. A small two-inch incision had been used. His pain, instability, and "snapping" were not relieved. On October 12, 1942, three months following the original arthrotomy, the right knee was explored through an adequate five-inch median parapatellar incision. The posterior one-third of the original medial meniscus was found still to be present and abnormally mobile. Upon flexion of the knee, it was observed to become displaced toward the center of the joint; it was excised. In the space formerly occupied by the previously extirpated anterior two-thirds of the meniscus, there was noted a small regenerated meniscus which consisted of a thickened and fibrosed invagination of the synovial membrane. This three-month-old rudimentary meniscus arising from an infolding of the synovia along the joint line was excised and sent to the pathology laboratory. Microscopic examination revealed it to consist of fibrous connective tissue, although grossly, except for its smaller size, it appeared quite similar to a normal meniscus.

The subject of regeneration of menisci following meniscectomy is one which had provoked considerable interest. Several investigators[3,4] have stated that the synovial membrane is the source of the regenerated menisci. Using dogs as experimental animals, Don King[5] observed a regeneration of fibrous tissue in meniscectomized knees. Gibson[6] reported a regenerated meniscus which revealed dense fibrous tissue microscopically, but no cartilage cells; the original meniscectomy had been done two months before the second arthrotomy. In our own case, the small regenerated meniscus definitely arose from an invagination of the synovial membrane filling the dead space left after meniscectomy. Apparently a metaplasia of the synovia into fibrous connective tissue had occurred.

Case II. A. J. C. This twenty-three-year-old white soldier gave a history of aching and discomfort about the lateral aspect of his left knee associated with a gradually progressive limitation of flexion. Examination revealed a tender cystic mass overlying the lateral aspect of the joint line. Flexion was limited at 90°, and three-fourths inch atrophy of the calf was observed. On November 27, 1942, the left lateral meniscus was excised. There was a large multiloculated cyst one and one-half inches by one and one-fourth inches by one inch in size arising from its periphery at the midpoint, which was lined by a smooth membrane and was filled with thick gelatinous material. A well defined pressure erosion of the lateral femoral condyle, lateral tibial condyle, and fibular head was evident; roentgenograms of the knee taken prior to operation had also revealed this. A full range of motion resulted.

Case III. M. W. C. This thirty-year-old soldier wrenched his left knee playing football in 1932. Two weeks prior to admission, as he was doing vigorous deep knee-bend calisthenics he experienced a sudden sharp pain on the inner side of the knee, and was unable to extend it fully. Arthrotomy on November 30, 1942, revealed the medial meniscus to be attached only at its anterior and posterior extremities. The coronary ligament was completely torn except at these points, and the meniscus was lying in an upside-down position, having rotated through an arc of 180°. Meniscectomy resulted in a normally functioning knee.

Case IV. V. E. Van W. This twenty-four-year-old white soldier pivoted on his left foot while playing an authorized game of basketball on November 14, 1942. He sustained acute pain about the inner side of the left knee which gave way, causing him to fall to the floor. Nine days later, his knee again gave way, and he fell to the floor, landing on his left patellar region. Thereafter, he was unable to flex the knee beyond 135°, preferring to hold it in full extension. Arthrotomy on December 7, 1942, revealed bloody synovial fluid in excessive amount. The posterior one-third of the coronary ligament and posterior attachment of the medial meniscus were torn, and the posterior extremity of the meniscus presented itself in

the intercondylar notch. A bony fragment one-half inch by one-half inch by three-eighths inch in size had been fractured from the inferior pole of the patella. This and the meniscus were excised. Following operation, a full range of free motion ensued.

Case v. A. A. L. This twenty-nine-year-old white soldier severely wrenched his left knee sliding into base while playing an authorized game of baseball on December 18, 1942. Thereafter it became swollen, painful, and unstable. "Snapping" and "clicking" were complained of. Arthrotomy on February 22, 1943, disclosed an oblique tear of the anterior one-third of the medial meniscus. The torn portion, still attached to the anterior extremity of the meniscus was crumpled up into a hard mass one-half inch by one-fourth inch by three-eighths inch in size. It had apparently impinged between the articular surfaces upon motion of the knee, as there was a groove one-eighth inch wide and nearly that deep gouged out of the articular cartilage of the medial femoral condyle; this groove was one and one-half inches in length, and coursed in an anteroposterior manner along the long axis of the condylar surface. Two similar small grooves had been gouged out of the corresponding articular surface of the medial tibial condyle, and the articular cartilage of the inferior pole of the patella was fibrillated. The medial meniscus was excised.

## CONCLUSIONS

A résume of fifty arthrotomies of knees of soldiers has been presented. Thirty-eight medial meniscectomies were done; twenty-one of these were for tears of the medial meniscus. Five lateral meniscectomies were done for cysts of the lateral meniscus. No tears of the lateral meniscus were encountered.

It is strongly believed that if an arthrotomy is indicated, an adequately large incision should be made and the joint thoroughly explored. It is also believed that if a meniscectomy is done, the entire meniscus should be removed. Quadriceps-setting exercises and assisted active motion on the first day after operation, and unassisted walking by the seventh day following operation, will hasten convalescence, and prevent quadriceps atrophy and weakness.

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Since this paper has been prepared, thirty-three additional knee joint arthrotomies have been done. Two tears of the lateral meniscus were encountered. They were oblique tears of the middle third.

# FURTHER EXPERIENCE WITH PILONIDAL CYSTS AT FORT SILL, OKLAHOMA

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OF impelling interest to the surgical departments of our Army hospitals is the continued appearance of the many soldiers for treatment of pilonidal cysts, sinuses and their complicating infections and abscesses. This condition is possibly due to the many hours spent by troops sitting on the hard wooden seats of benches and trucks, in tanks, jeeps, and saddles. This is an educated Army, so the men at a post like Fort Sill spend long periods of each day seated in class at school. This is also a mechanized war, so the men may be seated in vehicles of many types during the greater part of their time.

In addition, at Fort Sill, the home of the Field Artillery School, many physical examinations are done upon Officer Candidates. If a pilonidal sinus, evidenced by presence of a tumor mass or discharging sinus, is discovered, the man is usually informed that this condition must be remedied before he can enter the school. After the course of study is finished, another physical examination is done, and at this time a few more disqualifying cysts or sinuses may be discovered. These men, too, must submit to operation before being commissioned. This adds to the usual number of ordinary symptomatic cases coming in for operation.

It is agreed by all that complete excision of a pilonidal cyst, with all its sinuses and branches, is the prime requisite in its cure. However, disagreement enters as to how best to take care of the wound from this point on. The variety and number of procedures advocated is mute testimony to the fact that there is no one single perfect plan. It will readily be seen that variation in the size, shape, location and condition of these cysts as well as in the individual reaction of the patient, play a part in determining what should be done in any given case. Toward a solution of this problem are the following further experiences recounted:

## OPEN PACKING

In a previous article,[1] we reported our experience with this type of management. the average length of postoperative hospitalization was twenty-six days, varying in extremes from seven to fifty-eight days. Peculiarly enough, the discomfort suffered by these patients seems to be much less than that among civilians. Also, many men have been sent to full duty quite early with moderate sized wounds, requiring only a daily bath and a simple dry dressing. The use of sulfanilamide powder dusted into the wounds every two or three days seems to have been of some help in preventing or combatting secondary infection. This much may be said for the method, however, that it is one sure way of obtaining complete cure of the pilonidal cyst when the time factor is not considered too important.

## PRIMARY CLOSURE

The treatment of small, uninfected, asymptomatic pilonidal cysts or sinuses can usually be carried out surgically, as with any dermoid or sebaceous cysts elsewhere in the body. The cyst can be excised and the wound closed primarily, being careful to obliterate the dead space by using a figure-of-eight retention suture tied over a piece of gauze. We have done this on three occasions in the past few months with primary healing resulting. The patients did not suffer any postoperative pain or discomfort to speak of. Table 1 shows the pertinent features of these four cases.

It will be noted that the men were kept in the hospital two to three weeks postoperatively, which seems an unusually long period—and it is. They could all have been discharged after a few days, but were not sent out for two reasons:

1. We wished to make sure personally that healing was complete, that the wounds did not become infected secondarily, and that they did not open later. We are satisfied that if the silk sutures used are left in eight to ten days and the gauze pack kept in place with the retention suture that length of time, the wounds will heal cleanly and kindly.

2. The second reason for keeping these men in the hospital for this prolonged period is that all three of them were in the Officers Candidate School. This is a very hard course, with long periods of work in class and activity in the field. It is a course in which even a normally healthy man is put to the test. Then, too, there were administrative factors which kept a man in the hospital several, or many, days after he was ready for discharge, such as the waiting for the next class to start, and it was thought that the man was better off under direct observation than marking time in his quarters.

TABLE I

| Name | Size of Cyst | Date of Operation | Size of Original Wound | Date | Postoperative Days at Hospital | Primary Healing |
|---|---|---|---|---|---|---|
| King, S. | Small | 8-28-42 | ? | 9-16-42 | 19 | Yes |
| Robinson, R. | Moderate | 10-19-42 | 2 × 1 in. | 11-2-42 | 14 | Yes |
| Brown, H. | Small (1 × ⅓ in.) | 11-2-42 | 1 × ½ × ½ in. deep | 11-17-42 | 15 | Yes |
| Huitt, E. | Moderate | 11-18-42 | 2 × 1 × ½ in. | 11-28-42 | 11 | Yes |

### SKIN GRAFTING

Upon the suggestion of Lieut. Colonel B. L. Coley, in order to cut down the time for complete epithelialization, a trial at skin grafting of wounds in uninfected cases, at the time of the original excision, or later when cleanly granulating, would be given. In this connection, two important factors had to be given consideration: (1) maintenance of a clean wound, and (2) adequate pressure upon the skin-grafted area.

The unsanitary condition of the region with which we are dealing, between the nates and close to the anus, obviously makes the taking of skin grafts precarious. The site of the pilonidal cyst and, therefore, the excised wound, varies with each individual. If it is high up over the flat surface of the sacrum, one has an admirable site for obtaining even, continued and optimum pressure. If, however, the cyst is located low over a mobile coccyx, or laterally in a fatty buttock, or worse still, over the postanal musculature, the problem of securing adequate and continued pressure dressings for four to seven days is a difficult one.

However, in two instances of grossly uninfected cases, skin grafting was undertaken. (Table II.) In the first case, a large cyst was excised, with a resulting oval wound 4 inches long and 2½ inches wide. The skin was sutured down to the deep fascia, resulting in a wound 3 inches by 1½ inches. Eighteen pinch grafts were then taken from the thigh and applied with a sponge rubber pressure dressing. Most of the grafts took, but when the patient was discharged thirty-four days later, there was still a small granulating area, which took several weeks more to close. The second case was a smaller cyst

1½ inches long. After excision and suturing down of skin edges, a wound resulted needing only six small pinch grafts for covering. These did not all take, and at the time of discharge from hospital, fifteen days later, a small granulating wound was still present.

TABLE II
SKIN GRAFTING

| Case | Size of Cyst | Date of Operation | Size of Original Wound | Size of Partial Closure | Size at Discharge | Date of Discharge | Postoperative Days in Hospital | Date Closed Approx. | Days Till Closed |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Large | 8/26/42 | 4 × 2½ inches oval | 3 × 1½ inches | Very small | 9/29/42 | 34 | 10/10/42 | 45 |
| 2 | 1½ inches long | 9/7/42 | 1½ × 1 inch | 1 × ½ inches | Small | 9/22/42 | 15 | 10/6/42 | 29 |

These two cases turned out successfully, but were carefully selected for trial of this method. For the much extra time and effort spent in operation and after care of the patient by one "sympathetic" to the method, it could be seen that the healing time was not much shortened. Further, it is probably applicable to only a few of the patients.

### PRIMARY PARTIAL CLOSURE BY SUTURE OF SKIN TO FASCIA

A logical outcome of these experiences seemed to be a compromise between complete open packing of the wound and complete primary closure. Accordingly, primary partial closure of the wound by suture of the skin edges to the deep fascia and periosteum was given a trial. A brief description of our procedure similar to those of McFee,[2] and DePrezio[3] follows:

As clean a preoperative field as possible should be secured. If an abscess is present to begin with, it is drained, and the inflammation allowed to subside with warm moist compresses or sitz baths for five to ten days. If there is a draining sinus to start with, baths are given for a few days, and sometimes the cyst is also incised for better drainage. Spinal anesthesia for the final operation has been most satisfactory in practically all cases, using 100 mg. of novocaine crystals dissolved in 2 cc. of spinal fluid. A block dissection is done with excision of all side tracts. This usually leaves a large gaping wound. Hemostasis is secured with fine plain catgut ligatures. Sulfanilamide powder is sprinkled over the wound surface. Fine interrupted silk sutures are then used to tack the edges of the skin down to the deep fascia and periosteum covering the sacrum and coccyx. This procedure decreases the wound to about one-half its original size. A little more sulfanilamide is then dusted on and a vaseline pack applied with moderate pressure. This is left in place for about four days. The wound is dressed every two days after this by the medical officer, who sprinkles a little sulfanilamide powder on the wound at the time. Sutures are removed in six to eight days. Daily sitz baths are then started with the use of sterile dry gauze dressing after each one. No infections or abscesses under skin flaps have resulted. The men have a very comfortable postoperative period and are out of bed a few days after operation. Occasionally, touching up of exuberant granulations at the skin edge with a silver nitrate stick is necessary. The wounds have progressively closed with this regimen in from two to six weeks under our observation. In this group of cases (Table III) attention is again called to the prolonged postoperative hospital stay. This, as in the instances of

primary closures, is due to our curiosity about the wounds, the question of development or not of infection, the amount of tension and cutting through of sutures, and the progress of healing, with or without sitz baths, sulfanilamide powder and the frequency of change of dressings.

The follow-up is not as easy as it would first seem. This Post has an ever changing personnel. Men are shipped out to other assignments directly from the hospital or a few days after their discharge. It should be noted, too, that not all subjects with similarly sized wounds heal and close over at the same rate. There is a large variation, and this is especially true with the tendency to exuberant granulation, both clean and infected, to which this anatomical region seems to be subject.

TABLE III

PARTIAL CLOSURE OF SKIN TO FASCIA

| Case | Size of Cyst | Date of Operation | Size of Original Wound | Size after Part. Closure | Size on Discharge | Date of Discharge | Postoperative Days in Hospital | Date Closed Completely | Days Till Closed |
|---|---|---|---|---|---|---|---|---|---|
| 1 | ? | 9/7/42 | ? | ? | ¾ in. × ⅛ in. (small) | 10/1/42 | 24 | 10/7 | 30 |
| 2 | 2½ inches long | 9/14/42 | 3½ in. × 2 in. | 3 in. × 1½ in. | Small | 10/3/42 | 19 | 10/15 | 31 |
| 3 | ? | 9/23/42 | ? | ? | ½ in. × ⅛ in. (small) | 10/3/42 | 10 | 10/30 | 37 |
| 4 | 1½ inches dia. and deep | 10/5/42 | 2 in. × 1 in. × 1½ in. | 1 in. × ½ in. | ¼ in. dia. | 10/23/42 | 18 | ? | est. ? 25 |
| 5 | 1 inch dia. | 10/5/42 | 2 in. × 1½ in. × 1 in. | 1½ in. × ½ in. | 1 in. × ⅛ in. | 10/31/42 | 26 | | |
| 6 | ? | 10/9/42 | 3 in. × 1½ in. × 1 in. | 2½ in. × ½ in. | 2 in. × ¼ in. | 10/31/42 | 22 | | |
| 7 | 8 cc. | 10/9/42 | ? | ? | 1 in. × ¼ in. | 10/27/42 | 18 | | |
| 8 | ? | 10/14/42 | ..... | ..... | ½ in. × ¼ in. | 11/9/42 | 26 | | |
| 9 | ? | 10/15/42 | 2½ in. × 1½ in. × ¾ in. | 2 in. × ½ in. | 2 in. × ⅜ in. | 11/1/42 | 17 | | |
| 10 | ? | 10/17/42 | 4 in. × 3 in. × 1½ in. | 3 in. × 1 in. | ¼ in. dia. | 11/14/42 | 28 | | |
| 11 | ? | 10/12/42 | ? | ? | 2 in. × ⅛ in. | 11/2/42 | 21 | | |
| 12 | ? | 10/28/42 | 2½ in. × 1½ in. | 1½ in. × ½ in. | 2 in. × 1 in. | 11/9/42 | 12 | 12/16/42 | 49 |
| 13 | ? | 11/4/42 | 4 in. × 3 in. × 1 in. | 4 in. × 1½ in. | 2 in. × 1 in. | 11/27/42 | 23 | 12/6/42 | 32 |
| 14 | ? | 11/9/42 | 1½ in. × 1 in. × 1 in. | 1 in. × ¼ in. | 1 in. × ¼ in. | 11/22/42 | 13 | 12/24/42 | 45 |
| 15 | Long | 11/9/42 | 3½ in. × 1½ in. × 1½ in. | 3 in. × ½ in. | 2¾ in. × ¼ in. | 11/29/42 | 20 | 12/30/42 | 53 est. |
| 16 | Moderate | 11/23/42 | 1½ in. × 1 in. × 1½ in. | 1¼ in. × ⅛ in. | 1¼ in. × ¼ in. | 12/13/42 | 20 | | |
| 17 | Large | 11/20/42 | 3½ in. × 1½ in. × 1½ in. | 1½ in. × 1½ in. | 2 in. × ½ in. | 12/16/42 | 26 | | |
| 18 | Moderate | 11/23/42 | 2½ in. × ¾ in. × 1 in. | 2½ in. × ¼ in. | ..... | 12/16/42 | 23 | | |
| 19 | Moderate | 11/27/42 | 2½ in. × 1½ in. × 1 in. | 2 in. × 1½ in. | 1¼ in. × ½ in. | 12/15/42 | 18 | | |
| 20 | Moderate | 11/27/42 | 2 in. × 1½ in. × 1 in. | 1¾ in. × ¼ in. | 1½ × ¼ in. | 12/15/42 | 18 | | |
| 21 | Moderate | 12/7/42 | 2 in. × 1½ in. × ½ in. | 2 in. × ½ in. × 0 in. | 1¼ in. × ¼ in. | 12/26/42 | 19 | | |
| 22 | Small but deep | 12/7/42 | 1½ in. × 1 in. × 1 in. | 1¼ in. × ¼ in. × 0 in. | 1¼ in. × ¼ in. | 12/26/42 | 19 | | |
| 23 | Moderate | 12/14/42 | 1½ in. × ½ in. × ¾ in. | 1¼ in. × ¼ in. × 0 in. | Still in hospital | | | | |
| 24 | Moderate | 12/16/42 | 1¾ in. × 1 in. × 1 in. | 1½ in. × ¼ in. × 0 in. | Still in hospital | | | | |

The average length of postoperative stay in the hospital in this group of twelve cases was nineteen and one-fourth days. Three other patients, very recently operated upon, are not included in the above group. They could easily be discharged and sent to the dispensary for dressings, as were some of those original cases which were packed wide open to start with and sent to duty after eight to ten days' hospital stay postoperatively.

## REMARKS

There are two or three further problems in this study which should be considered.

Further, the question of recurrences cannot be completely settled at this early date. Probably six months after complete closure should elapse before one can say there is no recurrence only after thorough examination. Important, too, is the problem of the type of scar which results after each one of the procedures, whether it is tender, painful, friable, tough, comfortable and serviceable.

These experiences are merely those of one hospital for a period of fifteen months in only one field of a fairly busy surgical service. We wish it were possible to furnish more details and a more complete follow-up. Records of some cases are incomplete for all points which we now believe to be of importance for comparison. Seven different surgeons operated upon those patients. This made it difficult to standardize technic and to record all pertinent facts. A standard blank form for each case will probably yield this information for future reference and summary. We will also try to engage the interest of the eleven different dispensaries on this post in the postoperative care and records of these cases so that they may be followed to a shorter successful termination.

## CONCLUSIONS

1. The flap suture method with partial closure represents an advance in shortening the period of hospitalization.

2. The procedure of complete excision and packing represents a reliable method of management in the hands of the average surgeon when circumstances do not permit a selection of cases.

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# TENOSYNOVITIS*

## AN INDUSTRIAL DISABILITY

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WITH the speeding up of production in most types of work, it is obvious that it is the duty of the industrial surgeon to do everything possible to reduce disability in injured workmen. In order to test the efficiency of some of our methods of treatment, we are analyzing various groups of cases in order to determine whether or not our methods can be improved.

We have chosen the subject of tenosynovitis, a comparatively simple injury, but one that results in a great variation in length of disability. If we can determine why some patients recover in a few days while others are disabled for sixty days or more, apparently suffering from the same type and severity of trauma, we may be able to improve our method of treatment.

During a recent twelve-month period we treated seventy persons with a diagnosis of tenosynovitis, approximately .54 per cent of the total admissions for that period. The total time lost on account of disability of these seventy persons amounted to 1,222 days, or approximately three and one-third years, a rather surprising amount of time lost for a comparatively minor injury.

We divide our cases of tenosynovitis into three groups: first, those cases following strains of the wrist or ankle in which the tendons are overstretched; second, contusions to the tendons and sheaths, both of which classifications are considered as accidents; and third, a group which is becoming more common, in which irritation of the tendon and sheath follows repeated and rapid motion of the part, a condition which should be classed as an occupational disease. The above three types of tendon insult may occur in tendons apparently normal, or they may be superimposed on a tendon or sheath which has some pre-existing abnormality, perhaps an abnormality that has been entirely free from symptoms until some trauma or irritation brings it to the patient's notice.

The pathological status of tenosynovitis has not been demonstrated as completely as many other conditions because we seldom have the opportunity to examine the affected parts unless they require exploration. It is easy to visualize, however, the pathological picture occurring in a contused or overstretched tendon in which a few fibers may be torn, the presence of minute hemorrhage, edema and exudation producing more or less local swelling. It is quite difficult, however, to visualize the changes which take place in a tendon or its sheath following rapid or repeated motions. Moritz[1] describes the work of Obolenskaja and Goljanitzki in which they found in experimental animals, fraying of the surfaces of both the tendon and its sheath, accompanied by edema and interstitial hemorrhage, following rapid, repeated motions of the tendon. These changes are probably the beginning of narrowing of the sheath or adhesions between the sheath and the tendon, which are found occasionally on exploration.

Howard[2] explored three cases of crepitating tendons in order to study their pathological status. He found that in certain cases of direct blows over the leg or forearm, a crepitating swelling appeared. Exploration showed a jelly-like edema

* From the Indianapolis Industrial Clinic.

about the muscle-tendon junction, together with some muscle fiber degeneration.

The various latent abnormalities of tendons or their sheaths which may be aggravated by either trauma or repeated motions, are scar tissue changes, probably the result of previous injuries, and neoplasms. The scar tissue changes consist of slight swellings in the tendons, often accompanied by a constriction of the sheath at the corresponding level. Again, fibrous bands may form between the tendon and its sheath.

Tumors of the tendons and sheaths are quite rare. The most common of these is the fibroma, a true benign neoplasm. It may occur as a small round nodule on, or within, the tendon. A fibroma is not the result of trauma but it can become noticeable following trauma or excessive motion.

Some of the older texts describe tenosynovitis as being due to a "rheumatic condition." This may be true in some instances but we have never seen a case in which we could ascribe this etiology. It is possible, however, that a latent or cryptogenic infection, as of the teeth, sinuses, etc., might prolong recovery or even aggravate a traumatic tenosynovitis.

A ganglion of a tendon sheath does not properly come under the heading of tenosynovitis. Nevertheless, it is well to consider it at this point. We usually consider a ganglion as a hernial protrusion of the tendon sheath, a swelling which may appear spontaneously or may follow shortly after an injury. Pack[3] states that a ganglion is not a herniation of the sheath but is due to a fibroplasia and colloid degeneration which coalesce to form a cyst. Regardless of their pathology, we must admit that many ganglia follow trauma to the tendons of the wrist. There are a few other forms of tendon disorders that may be mentioned but which were not encountered in the cases under consideration. At times these must be kept in mind in making a differential diagnosis. There is the septic or pyogenic form of tendon sheath infection which follows infected wounds of the hands or wrists. Rarely we encounter tuberculous tenosynovitis or gonorrheal tenosynovitis, neither of which has any relation to trauma. The xanthoma is a nodular mass occasionally found on a flexor tendon of one of the fingers. It is a granuloma composed of various types of connective tissue cells intermingled with lipoid material. These growths are benign and it is questionable whether or not they are true neoplasms. Apparently they have no relation to trauma.

In the form of tenosynovitis under consideration, that is, those cases resulting from strains, contusions and repeated motions, pain, usually disabling, in the region of the affected tendon is the most constant feature. This is made worse on pressure over the part and also on using the member controlled by that tendon. Swelling of the tendon sheath can often be seen and palpated. It is unusual for the overlying skin to be reddened. In the majority of cases a tendon crepitation is marked and can either be felt or heard through the stethoscope. Occasionally, a clicking or snapping sensation is present as the tendon passes through its sheath. This is a most important finding. When it is present in an acute case it means that the abnormality has existed prior to the trauma, perhaps causing no trouble until aggravated by trauma or overuse. This clicking or snapping is the result of a scar tissue thickening or a fibroma of the tendon, usually associated with a constriction of the tendon sheath. Often these nodules and thickenings of the tendon can be palpated. In a few of our cases this clicking sensation was not present during the acute stage of the trouble but appeared later. This was probably due to an exudate within the sheath during the acute stage, which distended it to the point that the clicking could not be observed until after the acute symptoms had subsided.

The diagnosis of tenosynovitis offers no difficulty if one finds the clinical features enumerated above. That form of tenosynovitis following the excessive use of a

part has been confused with the so-called occupational cramps or palsies. The chief differential point is that in the case of an occupational cramp, the pain or disability occurs only when the patient is performing those motions required in his work. Making the same motions on examination causes no difficulty. In the case of tenosynovitis, the pain is present on motion under all conditions.

The treatment of acute tenosynovitis has been to put the part to rest by means of a plaster splint. This is removed about every second day in order to give the parts gentle passive motion to prevent stiffness, and also for the application of a diathermy treatment. After the acute symptoms have subsided, the patient is allowed to use the part for very slight movements only. When all pain has subsided the patient is allowed to resume his work gradually. Permitting patients to return to work too soon has been the cause of recurrence in several cases. When a clicking or snapping is noted, exploration is performed as soon as possible. When a distinct nodule is found, it is excised and the sheath repaired. When there is a fusiform swelling of the tendon with a constriction of the sheath, the latter should be "windowed" to allow free motion of its contained enlarged tendon.

In our present study of seventy cases of tenosynovitis, forty-four were attributed to strains, thirteen to contusions and thirteen to repeated motions, such as pushing material with the thumb and finger, repeated pressure on a part of a machine, turning screws, rubbing or polishing materials, etc.

The forty-four cases of tenosynovitis due to strain are distributed as follows:

| | |
|---|---|
| Extensors of the wrist or fingers at the level of the wrist | 32 |
| Flexors of the wrist | 2 |
| Extensors of the thumb | 4 |
| Extensors of the index finger | 2 |
| Flexor of the index finger | 1 |
| Extensors of the toes | 1 |
| Tendo calcaneus | 2 |

(While the tendo calcaneus does not possess a sheath, when strained and contused it can produce the same clinical features as sheathed tendons. Even crepitation is generally present.)

Out of this group of tenosynovitis due to strains, two patients were operated upon.

### CASE REPORTS

W. R., a male, age twenty-nine, strained his right wrist. After a few days the condition gave the appearance of a tenosynovitis of one of the flexors in the right wrist. With rest to the part the condition improved, but on returning to work the pain returned. Over a period of about three months he had thirteen days of disability and when working he had to limit his activities. During the fourth month following the injury a small nodule could be palpated on a tendon in the wrist proximal to the flexor retinaculum. This was explored and proved to be a true fibroma in the flexor indicis profundus tendon. Forty-four days following the operation he returned to work, free from symptoms. His long convalescence was occasioned by the necessity of severing the tendon and repairing it in the removal of the fibroma.

L. B., a female, age thirty, sprained the extensor tendons of the left thumb. She worked about one month without receiving treatment, and then splinting and diathermy treatment were used for fifty-six days with very little improvement and she was still disabled. On account of the persistent pain and tenderness. the tendon of the extensor pollicis brevis was explored. A constriction of the sheath was found distal to the annular ligament, with adhesions between the sheath and the tendon. The constriction was severed and the adhesions were broken up. The patient returned to work at the end of twenty-five days, free from symptoms.

The thirteen cases of tenosynovitis due to contusions can be grouped as follows:

| | |
|---|---|
| Extensors of the wrist | 8 |
| Extensors of the fingers | 2 |
| Flexors of the fingers | 2 |
| Extensors of the ankle | 1 |

Out of this group, three patients were operated upon:

F. L., a female, age thirty, had a contused flexor surface of the right wrist. She was given conservative treatment with short periods of

disability for about one year when a ganglion appeared over the flexor carpi radialis. Following removal of the ganglion she was able to resume work after thirty days.

J. W., a male, age thirty-nine, suffered a contused palm of the left hand. The diagnosis of tenosynovitis of the flexors of the left ring finger was made. After two weeks of conservative treatment there was no improvement. By this time the diffuse swelling which had appeared immediately after the injury, had subsided and a distinct nodule in the tendon could be palpated in the palm at the base of the finger. Exploration through the palm revealed a true fibroma of the tendon sheath, which was removed. The patient returned to work in thirty-five days.

P. J., a male, age thirty-three, contused and lacerated the palmar surface of the left wrist, the laceration not involving tendons or sheaths. Six weeks later he reported, complaining of a painful nodule in the tendon of the flexor carpi radialis in the middle third of the forearm. Exploration revealed a small true fibroma of the tendon, which was removed, followed by a relief of symptoms. He returned to work five days following the operation. In this case, in all probability the contusion brought to his attention the pre-existing fibroma.

The thirteen cases of tenosynovitis resulting from rapid or repeated motions are grouped as follows:

| | |
|---|---|
| Extensors of the wrist or fingers at the level of the wrist | 7 |
| Extensors of the thumb | 3 |
| Flexors of the thumb | 2 |
| Flexor of the middle finger in the palm | 1 |

Out of this group three patients were operated upon:

A. P., a female, age twenty-nine, for three months had used the right thumb to press an emery cloth against material in a lathe. Rather suddenly a trigger thumb appeared. Exploration showed a thickening of the tendon with a constriction of the sheath at the same level. Removal of the swelling on the tendon and leaving a window in the sheath relieved all symptoms. Microscopic study of the nodule showed scar tissue formation. One week of disability followed the operation In all probability this condition was the result of irritation of the tendon and sheath rom her occupation.

L. H., a female, age thirty-seven, complained of pain in the flexor surface of the right thumb following one month of work on an assembly line in which she constantly used the thumb, screwing caps on small shells. Examination showed a definite trigger thumb. Exploration revealed a bulging of the tendon with a constriction of the sheath at the level of the metacarpophalangeal joint. Part of the constriction of the sheath was excised, allowing free motion of the tendon. The patient was completely recovered fourteen days following the operation.

C. S., a male, age fifty, pulled trucks over uneven surfaces for six months. There appeared a gradually increasing pain in the palm of the right hand, increasing to the point of complete disability. Examination revealed a tender nodule in the palm, on the flexor tendon of the middle finger. Exploration showed a nodule on the tendon with adhesions to the sheath. The nodule was removed and showed microscopically to be a low grade inflammatory cicatrix. Postoperative disability amounted to twenty-eight days.

## SUMMARY

In summarizing our seventy cases of tenosynovitis during a period of twelve months, we find that sixty-two patients were treated by conservative methods and eight were operated upon. Of the sixty-two nonoperative cases, disability ranged from none to sixty days, a total of 933, or an average of fifteen days disability per case. Of the eight patients operated upon, disability before operation ranged from none to fifty-nine days, of a total of 119 days. The postoperative disability in these cases totaled 170 days, or twenty-one days per patient.

While statistics prove little or nothing, our collected figures suggest an improvement in our procedure. In all of our operative cases except one, exploration was done on definite physical findings, namely, the presence of a nodule on the tendon or the snapping or clicking on motion. In one case (L. B.) conservative treatment was employed for fifty-six days, and as little improvement was obtained, the tendon

was explored, showing a narrowing of the sheath with adhesions. In reviewing our cases in which we used conservative treatment, we find fourteen cases with a disability of more than twenty days, giving a total disability of 542 days, an average of thirty-nine days per case. Therefore, with an average convalescence of twenty-one days, even if we found nothing on exploration, we would have added nothing to the period of disability. Again, on exploring those cases which did not respond to conservative treatment within twenty days, we might find some organic condition that could not be determined on physical examination. From now on, we intend to explore all cases of tenosynovitis that do not show decided improvement within twenty days.

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The prognosis of gas-bacillus infection depends upon the patient's resistance, the part of the body involved, the virulence of the organism and the treatment. The extent of operative treatment depends upon the severity of the individual case.

# ANISOAURIA IN CONGENITAL TORTICOLLIS*

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OCCASIONALLY considerable difficulty is encountered in younger children in differentiating the side which is involved in congenital torticollis. The maternal impression as to position of head and chin differs frequently from the position the head is held at the time of the examination. Also in children with short necks or in very young children, in whom poor co-operation makes careful examination difficult, the determination of the side affected becomes more of a problem.

Assymetry of face and skull, which appear smaller on the side of the shortened muscle, if present, gives valuable confirmatory evidence. Another sign which I found of definite value is the underdevelopment of the ear on the affected side. The involved ear in some cases is only two-thirds or less the size of the normal ear. The discrepancy in the size of the ears has been found often to exist in the absence of facial assymetry and in such instances was of additional diagnostic significance. A return to near normal size does occur after successful correction of the torticollis but in some instances the difference was observed to persist for several years afterward. Also hypertrophy and flaring out of the ear on the unaffected side was observed in rare cases, so that this ear appeared much larger than the ear of a normal child of the same age.

The etiology is probably identical with the cause of the facial assymetry. Compression of the external carotid artery at the angle produced when the head is tilted to one side as a result of the torticollis has been suggested as one of the causes. A hematoma of the sternomastoid was found on examination in a number of our cases seen within a few weeks after birth and this was probably the immediate cause of the torticollis. It is possible, however, that the presence of antenatal fibrosis of the sternomastoid on the affected side was responsible for the tear of the muscle and production of the hematoma. The overgrowth of the ear on the normal side, whenever present, is believed to be due to an increase in blood supply to the facial and occipital arteries on the non-affected side, and possibly is in the nature of a compensatory hypertrophy which is seen in paired organs when the function of one is impaired.

This note has been prompted by the failure to find mention in medical literature of the occurrence of this difference in size of the auricular appendages in congenital torticollis. The term anisoauria is suggested for this condition.

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# Case Reports

## POTT'S DISEASE AFFECTING A SILENT AREA OF THE SPINE*

### CASE REPORT

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THE case herein reported is that of a diagnostic problem and demonstrates the difficulty of making the correct diagnosis when the lesion is located in a silent area of the vertebral column. No symptoms whatsoever were present, and the only evident physical sign is shown in the accompanying photograph. (Fig. 1.)

#### CASE REPORT

L. N. C., a Chinese male, age thirty-three, Hospital Register No. 15,583, was admitted to Station Hospital, Camp Shelby, Mississippi, August 15, 1941, with the chief complaint of swelling on the lateral surface of the left thigh.

The soldier stated that about July 15th, one month prior to admission, he first noticed a slight swelling over the lateral surface of the left thigh, at the level of the hip joint. No pain accompanied the swelling and no pain was noted on motion of his leg on the affected side. As his leg did not bother him, he paid no attention to the swelling. The tumor mass gradually increased in size until August 5th, about three weeks after onset, then suddenly began to increase rapidly in size, and continued to enlarge until he was admitted to the hospital. The soldier had no complaint other than the one described above; in fact he had no complaint—he "just thought something was wrong."

His past history revealed that in 1931 the patient was operated for ruptured peptic ulcer (note scar in photograph), no sequela. In 1938, he developed a primary penile lesion confirmed by a positive Wassermann reaction, and was treated continuously for eighteen months by hip and arm shots at weekly intervals. His family history revealed nothing of note except that one sister was operated for "tubercular breast."

Physical examination on admission revealed a well developed and fairly well nourished Chinese male, blood pressure 100/66. The patient was ambulatory and afebrile. His only reason for presenting himself for examination was the formation of a symptomless tumor mass of the left thigh. Examination of head, including eyes, ears, nose, and throat, was non-revealing. Examination of the chest showed nothing of note. Except for a healed, firm, upper right rectus incision, the findings on abdominal examination were within the limits of normal. No tender areas were noted over any of the vertebrae and no tenderness was present in either flank or groin. On inspection of the lateral surface of the left thigh at the level of the greater trochanter, a large tumor mass was noted. It was about the size of a "volley ball" and on palpation was found to be fluctuant and non-tender. The mass did not appear to be attached to the skin or deeper structures. No induration was present surrounding the mass, and no evidence of inflammation could be detected within the mass. There was no pain on motion or limitation of motion of the left lower extremity. The external genitalia were normal in size and development. Rectal examination revealed no strictures or ulcerations and the mucosa appeared normal. The lower extremities were well nourished; no atrophy, paralysis, or any deformity was noted. The reflexes were normal, equal, and physiological.

Complete blood picture and urinalysis were within the limits of normal. Blood serology was

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positive on repeated occasions. Spinal fluid was normal. Repeated *x*-ray pictures of the chest and vertebral column were reported as normal.

On September 5th, the tumor was injected with 50 cc. of 5 per cent solution of sodium iodide and *x*-ray pictures were made. However, visualization of the cavity was not successful.

Fig. 1. The tumor mass seen on lateral surface of left thigh was the only sign or symptom complained of by the patient. The mass measured approximately 8 inches in diameter.

On August 16, 1941, the tumor was aspirated and 500 cc. of thick, smoke-colored fluid was withdrawn, thereby reducing the cyst to about one-half its size. A specimen of the aspirated material was sent to the laboratory for smear and culture and no growth was reported. However, a Wassermann examination was done on the material and reported by the laboratory as positive.

On August 22nd, the cyst was again aspirated and 800 cc. of the same type fluid obtained. The specimen was sent to the laboratory and was again reported, "no growth."

A third aspiration was done on August 30th, and 500 cc. of fluid was withdrawn. No change in the consistency of the material was noted as compared with that previously withdrawn.

On September 3rd, a genitourinary consultant advised antiluetic treatment for latent syphilis.

On September 10th, the tumor was once more aspirated and 500 cc. of fluid withdrawn. No changes were noted in the consistency of the fluid on gross inspection. As a result of consultation with members of the surgical staff, exploration of the tumor was decided upon with the possibility of finding some type of bizarre cyst. During this month of hospitalization the patient had remained free of symptoms and was ambulatory most of the time.

The tumor mass was opened on September 16th, and a large amount of smoke-colored fluid escaped from the tumor. The cystic mass was found to communicate with an opening posterior to the left hip joint and not with the joint proper. The wound was packed with iodoform gauze and sutured. It drained profusely until September 28th, at which time the sutures were removed. The lower third remained unhealed and continued to drain.

On the evening of October 15th, the patient developed a feeling of general malaise and aching of the entire body. On the morning of the 16th he had developed facial edema and temperature of 102°F. The wound was dressed and 200 cc. of light yellow fluid of a homogeneous, watery consistency escaped from the wound. On October 17th, the temperature was 103°F. and patient appeared to be definitely acutely ill. The patient's temperature, respiration, and pulse continued to mount, and his condition became critical on October 18th. The patient's course was progressive; temperature 105°F., delirious, comatose, moribund. He expired on October 19, 1941, at 10:55 A.M. despite all emergency measures employed, including continuous oxygen, blood transfusions, and cardiac stimulants.

The autopsy findings are quoted as follows:

"*External Examination.* The body is that of a well developed and fairly well nourished white male, 33 years of age. The pupils are round and equal and are neither dilated or contracted. The thyroid is not palpable. The chest is natural in contour. The abdomen is flat. The external genitalia are those of the normal male. There is a partially healed incision about 15 cm. long extending perpendicular to and over the greater trochanter of the left femur. The skin has healed on the upper half of the incision. In the lower half the edges are widely separated. Through this incision a tract may be palpated extending posterior to the femur and anterior to the sacrum. The walls of this tract are covered with dark grey exudate. There is extensive dark purplish-blue discoloration of the skin involving the face, trunk and extremities. The discoloration is most marked over the back of the shoulders. It is more marked on the left thigh than on the right. There is no recognizable subcutaneous edema.

"*Peritoneal Cavity.* The peritoneum is moist, smooth and glistening. There are numerous dense adhesions about the stomach. These are most marked about the pylorus. There are dense adhesions between the upper surface of the left and the right dome of the diaphragm. The dome of the diaphragm is at the level of the 4th rib on the right and the 4th interspace on the left.

"*Pleural Cavity.* The pleura is moist and smooth. The lungs are free in the pleural cavity, except for a few dense adhesions between the apex of the right lower lobe and the posterior chest wall.

"*Pericardial Cavity.* The pericardium is moist and smooth. There are no adhesions. The cavity contains no excess fluid.

"*Heart.* The heart is about natural in size and contour. The epicardium is smooth. The myocardium is dark brownish-red, the brown being somewhat more marked than is natural. The muscle is somewhat softer and more friable than is natural. The walls of all chambers are about natural in thickness. The endocardium is smooth and the valve cusps grossly natural. None of the rings are dilated. The cusps of the aortic valve are not separated. There is a slight thickening of yellowish discoloration of the endocardium just below the aortic cusps. The first few cm. of the aorta shows no pathological change. There is considerable longitudinal wrinkling of the intima of the descending aorta along the origin of the intercoastal arteries.

"*Lungs.* The lung tissue is dark reddish-grey, heavy, and subcrepitant. There is a semi-firm nodule about 6 mm. in diameter located 1 cm. deep to the pleura in the upper lateral portion of the right lower lobe. No other nodule and no areas of consolidation are found. The hilus and tracheobronchial lymph node are not involved.

"*Liver.* The liver is about normal in size and contour. The capsule is smooth except where already described adhesions were broken. The tissue is yellowish-brown and about natural in consistency. The lobular markings are distinct but not unusually prominent. The gallbladder is grossly natural.

"*Spleen.* The spleen is moderately enlarged. Estimated weight is 150–175 gms. The capsule is smooth and thin and the borders are slightly rounded. The tissue is relatively firm. The cut surface is dark reddish-purple. The lymphoid follicles are quite prominent. Only a small amount of pulp adheres to the knife on scraping.

"*Adrenals.* The adrenals are natural in size, contour and gross appearance.

"*Kidneys.* The kidneys are about natural in size, contour and consistency. The capsule of each strips easily, leaving a pale, red, smooth surface. On section the cortico-medullary markings are distinct. The vascular markings are grossly natural. The right ureter is moderately dilated. The left is not. Neither kidney pelvis shows any pathological change.

"*GI Tract.* 2 cm. below the pyloric ring on the posterior surface of the duodenum is a

small irregular crater with a smooth fibrous base. The crater is about 1 cm. in greatest diameter. There is no evidence of acute inflammation about the crater. The remainder of the GI tract shows nothing unusual.

"*Pelvic Organs.* Show nothing unusual.

"*Head.* The scalp and calvarium are grossly natural. The dura is smooth. The fluid in the subarachnoid space is clear. The brain shows nothing unusual.

"*Sinus Tract.* The sinus tract is large enough at its nearest point to admit the index finger passing from the wound on the left side posterior to the left femur and anterior to the sacrum, and it communicates with an abscessed cavity which is located upon the anterior surface of the sacrum. The cavity extends upward posterior to the peritoneum and medial to each psoas muscle as high as the 4th lumbar vertebrae. The anterior surface of the sacrum is roughened; otherwise, the bones show no grossly recognizable pathological changes. The spinal canal was opened by chiseling through the body of the 4th lumbar vertebra. Its lining was found to be smooth, and its contained fluid clear.

"*Anatomical Diagnosis.* 1. Tuberculous osteomyelitis of the 2d and 3d sacral vertebra with psoas abscess, left. 2. Luetic aortitis. 3. Passive congestion of lungs, marked. 4. Hydroureter, right, mild."

COMMENT

The small solitary nodule in the lung was found, on microscopic examination, to be tuberculous. A piece of bone taken in the region of the 2d and 3d sacral vertebrae was also found to be tubercular on microscopic examination at our laboratory here at Camp Shelby, Mississippi, and confirmed at the Army Medical Center, Washington, D. C.

A brief description of the microscopic findings of the bone slide follows:

"Sections of the sacral bone reveal extensive necrosis where the trabeculae are granular, devoid of cells and without the usual caseous markings. The adjacent marrow spaces are filled with shadowy and vaguely cellular necrotic material. The marrow spaces which are outside of the necrotic lesions are filled with connective tissue, lymphocytes, remnants of bone marrow and a granulation tissue which is infiltrated with lymphocytes and monocytes. In some places these cells form small tubercles which often have caseous necrotic cores. There are also occasional foreign body giant cells of the Langhans type."

# PRIMARY SARCOMA OF THE URETER

## CASE REPORT AND REVIEW OF THE LITERATURE

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REPORTS of primary sarcomas of the ureter are so rare that review of the literature is comparatively easy. The first case was reported by Ribbert in 1886—a spindle cell sarcoma in a girl four years of age. It arose primarily from the renal pelvis and contained numerous layers of striated muscular fibers.

Lichthin and Willinly have described a case of "alveolar" sarcoma of the ureter; Target and Meller (1920) have described a case of round cell sarcoma. Neumirth (1928) described a spindle cell sarcoma about the size of a walnut found in the lower third of the ureter in a male aged fifty-one.

Stewart and Kummel, quoted by D'Aunoy and Zoeller (1930) agreed that only five cases of sarcoma existed in the literature at the time of their review.

In a more recent review of the problem of malignancy of the upper urinary tract by George Gilbert Smith (1935) two cases of fibrosarcoma and one case of leiomyosarcoma are reported by Smith as personal cases but he stated that it was impossible to determine whether the primary tumor was in the kidney or ureter. Sarcoma primary in the kidney is not as rare as the above scarcity would indicate, and one would consider from Smith's remarks that these cases were primarily renal sarcomas.

Search of the literature since this report has failed to disclose other cases of primary ureteral sarcoma, so that we believe that the present case represents the sixth known report of primary sarcoma of the ureter.

Location of the tumor in the other cases has varied; two reported near the kidney, two about two inches from the bladder and not stated in one. Symptoms have varied from hematuria, to pain and discovery of mass; and the size of the tumor has varied from that of a walnut to that of a grapefruit. Age has varied from four to fifty-three years.

### CASE REPORT

Mrs. L. S., aged fifty-nine, a white woman, was admitted to my service at the Peninsula General Hospital of Salisbury, Maryland, on December 9, 1941. She was referred by Dr. John Yeaman. Her chief complaint was that of a heavy dull ache in the upper, left side of the abdomen, gas, and a lump in her side.

She had been well until July, 1941, when this aching sensation first appeared, accompanied by a sense of pressure and much belching of gas. The pain was at first intermittent and became progressively worse. The month before admission she first noticed the mass which felt like a ball. This had progressively increased in size and had become very tender, feeling to her to be the size of a grapefruit. She felt that the mass throbbed constantly, a sensation which was temporarily relieved after a bowel movement.

There had been no hematuria, frequency, or nocturia and no pain in her back. She had been constipated most of her life, and this had increased in the past few months. There was no history of passing blood by bowel. There was no history of indigestion and ingestion of food had no effect upon the pain.

The past medical history was negative: no serious illnesses, accidents or operations. The menopause occurred at age fifty-four, with no bleeding or discharge since. She had had eight children, three of whom were dead; one of tuberculosis and diabetes.

Her father and mother died at the age of seventy-three of apoplexy and Bright's disease, respectively; five sisters and one brother were living and well; one brother died of heart disease and one sister died of hypertension.

Physical examination showed a pale, elderly, white female of average nutrition. Blood pressure 174/102; temperature 98; pulse 84; respiration 20. The examination was negative except for complete adentia and the abdominal findings. The abdomen was dome shaped with normal liver dullness. There was considerable distention with gas. A large, smooth, clearly defined mass was palpable in the upper, left quadrant. The mass was not attached to the anterior abdominal wall and did not seem fixed in that it could be moved about 1 inch in all directions. It was very tender, especially at the upper pole. It seemed to be about the size of a large grapefruit and occupied all the left, upper quadrant. It could not be palpated posteriorly and there was no posterior tenderness. Pressure on the mass caused definite pulsation to occur, transmitted probably from the aorta. The remainder of the physical examination was negative.

Laboratory studies showed the following: hemoglobin 80 per cent; red blood cells, 4,070,000; white blood cells 4,350; neutrophiles 72 per cent; lymphocytes 28 per cent; blood urea 54 mg., urea nitrogen 25 mg., blood platelets 345,750. Prothrombin time 27 seconds. Fragility test showed hemolysis to begin at 0.46 per cent ant to complete at 0.34 per cent. Repeated urinalyses showed no red blood cells; two to six white cells and showed no abnormality either grossly or microscopically.

Fig. 1. Intravenous pyelogram. The mass is shown with moderate degree of hydronephrosis. The ureter is shown a short distance within the mass.

Fig. 2. Intravenous pyelogram which shows an abrupt ending of the ureter within the mass.

An intravenous pyelogram by Dr. Jack K. Williams showed a moderate hydronephrosis on the left side. On the right side there was a moderate ptosis of the kidney with some kinking of the ureter. The left ureter showed an abrupt ending within the tumor mass on some pictures. (Figs. 1 and 2.)

The barium enema was negative. All abdominal films showed the outline of a rounded mass in the upper left quadrant. (Fig. 3.)

After these findings and study, operation was planned as an exploratory laparotomy. Five hundred cc. of blood was drawn from a suitable donor before the operation began.

Operation was performed on December 12, 1941, under nitrous oxide, oxygen and ether using the closed method. A left, rectus incision was made in the upper part of the abdomen. There was a large, smooth mass 12½ cm. in diameter, spherical in shape, located beneath the left kidney and retroperitoneal in position. It was well supplied with blood, a large vein being attached to the left renal vein directly.

It was well encapsulated, freely movable and no metastasis was apparent. The left ureter went directly through the center of the growth.

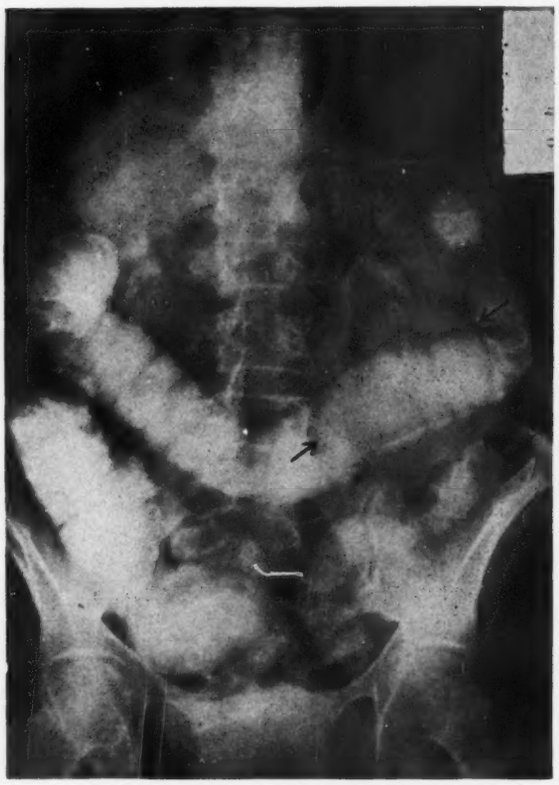

FIG. 3. Barium enema showing the transverse colon in front of the mass. The descending colon is pushed far laterally.

The posterior parietal peritoneum was loosely attached to the growth capsule. Some fibrous tissue also loosely attached the growth to the lower pole of the right kidney, but this was only loose areolar tissue. The only firm attachment, therefore, was to the ureter which coursed through it from an area about 1 inch beneath the kidney pelvis to about three inches from the bladder.

The intestines were packed away from the operative site. A vertical incision was made in the posterior peritoneum, two inches to the left of the midline. The growth was then carefully removed until its only attachment was to the large vein to the renal vein, and to the ureter. At this time the vein tore, although great care had been exerted to prevent just this accident. A large amount of hemorrhage occurred in a few seconds before the renal pedicle could be clamped. The kidney was then removed and the ureter dissected to its entrance to the bladder and also removed. Blood transfusion was started an instant after hemorrhage occurred, and a second transfusion was given immediately after completion of the first. The kidney pedicle was ligated with four chromic catgut ligatures, the ureteral stump ligated and carbolized, and the posterior peritoneum closed with catgut. Two Mikulicz drains were placed to this incision and the anterior wall incision closed in routine manner, using stainless steel wire to close the anterior fascia.

The blood pressure dropped to zero and the pulse became imperceptible for a period of three minutes after the hemorrhage, but rose rapidly as a result of the transfusion and the patient left the operating room in fairly good condition.

Shock treatment was carried out and convalescence was entirely uneventful. Drains were removed on the third day. A 500 cc. transfusion was given in divided doses on the second and third postoperative days. On December 12, 1941, her blood count was as follows: hemoglobin, 82 per cent; red blood cells 4,240,000; white blood cells 7,800 with normal differential. She was discharged on the fourteenth postoperative day in good condition.

Pathologically, the specimen consisted of a globial solid tumor measuring 12½ cm. in diameter, which had a firm fibrous consistency and on section showed a uniform structure. The growth was well encapsulated and no break in the capsule was present, except for ureter which coursed directly through the mass and to which the mass was attached.

Microscopically, it was diagnosed leiomyosarcoma. (Figs. 4 and 5.)

Sections were submitted to Dr. Howard J. Maldeis, of Baltimore, Maryland, and Dr. Albert Bothe, of Philadelphia, Pennsylvania, and this diagnosis was corroborated by both pathologists. Dr. Maldeis added that many parts of the sections showed myxomatous changes.

Routine follow-up examination on March 24, 1942, showed no symptoms. The patient had mild coryza for two days. She had gained five pounds in weight since the operation. Her present weight is 129. The incision was well healed and there was no evidence of recurrence and no urinary symptoms.

Follow-up examination on February 6, 1943 revealed that the patient had gained steadily in weight, her weight at that time being 137½ pounds. The incision remained well healed.

There were no symptoms of recurrence or metastasis. Palpation and percussion revealed no tenderness, masses or liver enlargement and there were no urinary symptoms. Blood pressure was 150/80. *X*-ray of chest was entirely negative for metastasis.

FIG. 4. Microphotograph under low power.

FIG. 5. Microphotograph (high) showing myxomatous degeneration and smooth muscle strands.

## CONCLUSION

We have herewith reported a case of leiomyosarcoma of the ureter which represents to the best of our knowledge the sixth reported case of primary sarcoma of the ureter. The marked features of the growth were its relatively few symptoms, its large size without obvious metastasis, its good encapsulation and its low index of malignancy. The difficulties in diagnosis are obvious because of the negative laboratory and *x*-ray findings. Ready and easy removal complicated by violent hemorrhage for which the surgeon had completely prepared and smooth postoperative convalescence characterized the operative procedure. It is yet too early to discuss the final end result, although in comparison to the average sarcoma, fourteen months without detectable recurrence or metastasis indicate a fairly hopeful prognosis.

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The commonest cause of delayed union in closed fractures is inadequate splinting. Fractures in certain locations as the neck of the femur and the wrist joint unite more slowly than the average. Most cases respond to further immobilization and frequent applications of heat.

# TRAUMATIC ARTERIOVENOUS FISTULA OF THE BRACHIAL ARTERY AND VEIN*

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TRAUMATIC arteriovenous fistulas occur less frequently in the great vessels of the neck and upper extremity than in the vessels of the lower extremity.[1–7] Common locations for arteriovenous fistulas are between the common carotid and jugular vein, the interval carotid artery and cavernous sinus, the femoral artery and vein, and between the axillary artery and vein.[8] Mason[9] collected fifty-nine cases involving the subclavian, and Mason and Pool[10] reported in a series of fourteen cases two involving the subclavian and two the brachial arteries. Matas[11] recorded two cases of arteriovenous fistula of the brachial artery and vein. Andrus[12] has recorded traumatic arteriovenous fistula of the palm and quotes Lyle as stating that there are sixty-six such cases reported.

The pathological and pathological physiological effects of an arteriovenous fistula have been investigated and reviewed by others.[13–16] Dilatation and hypertrophy of the heart and later cardiac decompensation with peripheral edema and ascites may occur. There is also an increased blood pressure and tachycardia, increased blood volume, diminished peripheral resistance at the site of the fistula, and abnormal oxygenation of blood due to admixture of venous and arterial blood at the site of the fistula. Brenham's tachycardiac sign is well known. There is a usually good collateral circulation developed when arteriovenous fistula is present. Venous pressure readings at the site of the fistula and, particularly, comparison of the well and affected side and arteriography in selected cases may aid in definitely establishing the diagnosis.

## CASE REPORT

J. C., a male, age six, was admitted to Metropolitan Hospital January 2, 1941 because of a peculiar buzzing sensation in the child's right arm. This began approximately eighteen months before. At that time, the patient fell on a broken milk bottle and sustained a laceration of the right arm 1½ cm. above the medial epicondyle of the right humerus 0.6 cm. long. A local physician closed the laceration with two skin clips without any further investigation of the injury. The parent stated at the time of the injury that the child lost a large amount of blood and looked very pale and weak. The hemorrhage was only controlled when a neighbor applied a tourniquet. The bleeding was also described as bright red color and spurting.

The skin clips were removed on the fifth day following the injury; the wound apparently healed by primary union. The patient was asymptomatic until approximately six months later when the child's mother noticed a peculiar buzzing sensation in the region of the injury. The parents believed this condition would gradually disappear and no physician was consulted at the time. The child during this period of time exhibited no unusual symptoms, playing with his friends and showing no signs of cardiac embarrassment. No local signs were apparent in the right upper extremity, excepting the buzzing sensation.

The patient had an occasional cold and sore throat. He had been unable to gain weight, but the remainder of systems were noncontributory.

Examination of the head revealed a small 2 cm. laceration of the right occipital region which apparently was healing well. Extraocular movements of the eyes were normal; pupils were round, central, and equal; they reacted promptly to light and accommodation. There was no obstruction or discharge in the ears and the tympanic membranes were normal.

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A crusting was noted in the anterior nares with slight serous discharge. There were numerous small areas of caries in the teeth. The pharynx was slightly injected; there was no postnasal discharge. The tonsils were hypertrophic and cryptic. The trachea was in the midline; there was anterior cervical adenopathy bilaterally. The chest was symmetrical and expansion equal; there was no dilation of the superficial veins. The lungs were resonant, tactile, and vocal fremitus was normal; breathing was vesicular—inspiratory "cogwheel"—no râles were noted.

The heart showed a visible apex pulsation in the fifth interspace 2 cm. to the left of the midclavicular line, and the maximum apex beat was palpated at the same point. Heart percusses were slightly enlarged, rhythm was regular, the rate being 100. Sounds were forcible and of good quality. There was a faint systolic murmur heard at the apex. Blood pressure: right arm 100/0, left arm 98/52.

The abdomen was symmetrical and moved readily with respiration. There were no scars or visible masses and no dilation of superficial veins. There was no spasticity and no tender points to palpation. The liver, spleen, and kidneys were not palpable. There was no evidence of hernia. There were bilateral small, freely movable glands palpable. The genitalia revealed constriction of the prepuce. The scrotum and testicles were normal. The rectum was not examined. The lower extremities were normal; reflexes were physiological.

The upper-left extremity was apparently normal, although it did show readily visible superficial veins on the anterior surface of the forearm and at the cubital fossa.

The upper-right extremity was apparently normal in size and shape. Dilated veins in the forearm and arm were noted on the anterior and medial surfaces. On close inspection, there was slight pulsation visible in the superficial veins which was synchronous with the apex beat of the heart. There was also noted a small white scar 0.6 cm. in length on the medial surface of the arm 1.5 cm. above the crease of the elbow. There was no clubbing of fingers, no visible capillary pulsations of finger tips, no cyanosis with arms level, depressed, or raised. There was a thrill palpable from a point 2 cm. below the elbow crease extending along the anterior and medial aspects of the arm and was palpable throughout the arm, in the axilla, and also in the supraclavicular region. The maximum area was 5 cm. long extending from the scar previously described. Superficial veins in this area when palpated pulsated synchronously with the apex beat of the heart. By means of auscultation a loud roaring bruit was heard synchronous with the apex beat of the heart from a distance of 5 cm. below the elbow crease along the anterior and medial surfaces of forearm and arm. This was also heard in the axillary and supraclavicular regions. The maximum point of intensity was about 3 cm. above the scar previously described.

COMPARATIVE MEASUREMENTS OF UPPER EXTREMITIES

| Circumference | Right, Cm. | Left, Cm. |
|---|---|---|
| Above biceps | 16.2 | 15.6 |
| Midbiceps | 16.5 | 16.0 |
| Below biceps | 16.0 | 15.4 |
| Elbow | 16.0 | 16.0 |
| Midforearm | 15.5 | 15.0 |
| Wrist | 12.0 | 11.8 |

| Length | Right, Cm. | Left, Cm. |
|---|---|---|
| Tip of acromion to tip of middle finger | 52.5 | 52.5 |
| Tip of acromion to tip of olecranon | 19.5 | 19.5 |

When arms were level, the right radial pulse felt slightly weaker than the left, and there was a suggestion of Corrigan "Water Hammer pulsation." When the arms were raised, pulsation were about equal, and the "Water Hammer" sensation was increased. When the "fistula" was obliterated by direct pressure, pulsations were about equal.

When arms were level, pulse was regular, and the rate was 100 per minute. When the right arm was raised, the pulse rate fell slightly —rate 92 per minute. When the "fistula" was completely obliterated by direct pressure or the application of a cuff, the radial pulse rate came 80 to 82 per minute.

Blood pressure was difficult to determine accurately in the right arm but the average of many readings was 100/0. The left arm was 98/52. When the right arm was raised and pressure taken on the left, there was a slight

rise in the diastolic, but no appreciable change was noted in the systolic value 98/60. When the "fistula" was obliterated by direct pressure or the application of a cuff, there was a marked rise in diastolic but only slight in the systolic 102/80. Blood pressures of both lower extremities were recorded as equal 108/62.

COMPARATIVE SKIN TEMPERATURES: ROOM TEMPERATURE: 23.5°C.

| | Right | Left |
|---|---|---|
| Wrist | 34°C. | 35°C. |
| Forearm | 34°C. | 35°C. |
| Elbow | 35°C. | 36°C. |
| Biceps | 35°C. | 36°C. |

Temperatures were taken on volar surfaces. Also numerous points were tested in the region of the scar, and the dilated superficial veins, but no local variations were noted.

COMPARATIVE OSCILLOMETRIC READINGS

| Pressure | Right | | Left | |
|---|---|---|---|---|
| | Arm | Forearm | Arm | Forearm |
| 110 | 1.0 | 0.5 | 0.5 | 0.5 |
| 100 | 3.0 | 1.0 | 0.5 | 1.0 |
| 90 | 4.0 | 1.5 | 1.0 | 1.0 |
| 80 | 7.0 | 2 | 1.5 | 1.0 |
| 70 | 10.0 | 4 | 2.0 | 1.5 |
| 60 | 11.0 | 4 | 3.0 | 2.0 |
| 50 | 12.0 | 4 | 2.0 | 2.0 |
| 40 | 8.0 | 3 | 1.5 | 1.5 |
| 30 | 6.0 | 2.5 | 1.0 | 1.0 |
| 20 | 4.0 | 2 | 1.0 | 1.0 |

Intradermal wheals of histamine were raised with 0.1 cc. of 1-10,000 on both upper extremities on the volar surfaces at the following levels; wrist, midforearm, elbow and midbiceps. There was an immediate response at all points with the wheals measuring 1.0 cm. in diameter and the surrounding "flares" measuring 4.0 to 5.0 cm. in diameter.

Direct venous pressure readings were taken from veins of right forearm at the elbow in the region of the scar. Attempts were made to select veins that pulsated. Pressures were not excessively high; the highest recorded was 15 to 16 cm. of water.

Circulation time was tested by injecting 0.5 cc. of alpha lobelein into a vein of the right forearm in the region of the scar. An attempt was made to select a vein that pulsated. From the time of injection till the patient coughed was about 6 seconds.

LABORATORY DATA

| | 1/2/41 | 1/3/41 |
|---|---|---|
| *Urinalysis:* | | |
| Color | Yellow | Yellow |
| Appearance | Cloudy | Cloudy |
| | 7.5 | 7.5 |
| Specific gravity | 1.018 | 1.018 |
| Albumin | Negative | Negative |
| Glucose | Negative | Negative |
| White blood cells | Few | Few |
| Epithelia cells | Few | Some |
| *Hemogram:* | | |
| Hemoglobin | | 90% |
| Erythrocytes | | 4,500,000 |
| Leucocytes | | 7,050 |
| Mature polymorphonuclear leucocytes | | 46 |
| Immature polymorphonuclear leucocytes | | 4 |
| Lymphocytes | | 49 |
| Monocytes | | 2 |
| Eosinophiles | | 2 |
| Basophiles | | 1 |
| *Blood Chemistry:* | | |
| Sugar | 75 | |
| Nonprotein nitrogen | 29 | |
| Creatinine | 1.3 | |
| Carbon dioxide combining power | 48 Volumes Per Cent | |
| Chlorides plasma | 530 | |
| Blood Sedimentation Rate | 15 Minutes-0 | |
| | 1 Hour-4 mm. | |

Blood from the right arm was taken from pulsating vein in neighborhood of the fistula. Blood from the left arm was taken from vein in cubital fossa. Oxygen determinations were as follows:

*Right Arm:* Content of Oxygen:
15.51
15.44
*Right Arm:* Saturation:
88.7%
*Left Arm:* Content of Oxygen:
13.54
13.37
*Left Arm:* Saturation:
77.0%
Capacity of Oxygen:
17.61
17.60

*X*-ray examination of the chest and upper extremities revealed the following: The lung fields were equal in illumination. The hilar and bronchovesicular markings were exaggerated. The costophrenic sinuses were clear. The diaphragmatic domes were smooth and the cardiovascular shadow was normal. The radio-

graphic examination of both upper extremities showed no variation from the normal in the osteology or soft tissue structure.

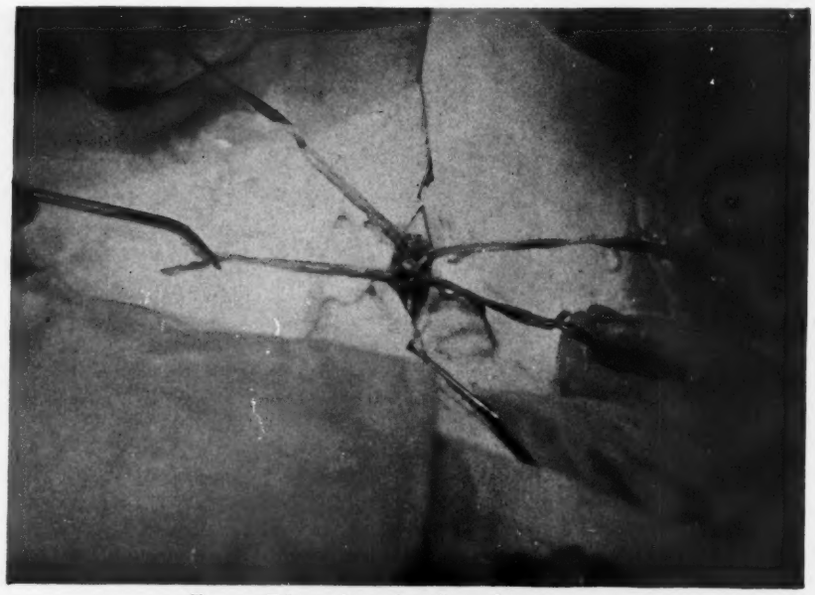

Fig. 1. Dissection of H-shaped aneurysm.

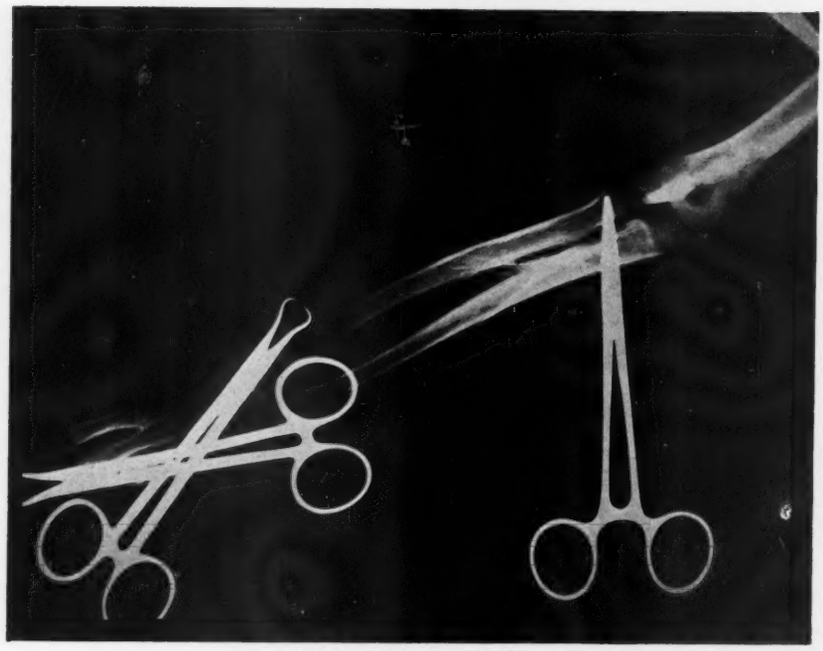

Fig. 2. Visualization with hippuran.

REPORT OF ELECTROCARDIOGRAM JANUARY 3, 1941

| | |
|---|---|
| Auricular rate | 110 per min. |
| Ventricular rate | 110 per min. |
| Interpretation: Sinus tachycardia | |
| P-R Interval | .14 Sec. |
| Q. R. S. Interval | .06 Sec. |

REPORT OF ELECTROCARDIOGRAM JANUARY 10, 1941

Interpretation: Sinus tachycardia

Operation was performed on January 4, 1941. The preoperative diagnosis was arteriovenous fistula of the right brachial artery and vein. The operative diagnosis was the same.

The skin was prepared with tincture of methiolate. An incision was made along the medial border of the biceps proximal to the original penetrating wound, down through the deep fascia isolating the brachial artery and vein. The incision was continued distal to the original wound, again isolating the brachial artery and vein. Numerous small veins connecting with the brachial vein were isolated and in some instances ligated in order to

visualize the field better. The median nerve appeared in the field and was carefully protected. The arteriovenous fistula appeared in an H-shape configuration (Fig. 1), showing a definite connection between the brachial artery and vein. Venous pressures were taken and recorded as follows: 28 cm. of water in the brachial vein. Proximal and distal tourniquets were placed on the arm and forearm and 15 cc. of hippuran was injected intravenously into the brachial vein, the distal tourniquet released, and roentgenograms taken. (Fig. 2.) Proximal and distal ligations in relation to the aneurysmal sac were done on the brachial vein, and the aneurysmal sac was ligated close to the brachial artery with two ligatures of black silk. Silk technic was used throughout. The wound was closed with interrupted black silk sutures.

Postoperatively, the patient was in good condition. Pulse 130; blood pressure 102/60, left arm. During and immediately following operation, he was given 500 cc. of 5 per cent dextrose in physiological saline. In the afternoon of the same day the pulse was 120, regular and of good quality; there was no staining of the dressing. The child reacted from anesthesia and took small sips of fluids by mouth, was quiet and apparently comfortable. On January 6th, there was very slight edema of the right hand, pulse 84; temperature 99.4°F. On January 8th, the dressing was removed and there was slight edema of the arm noted. The wound was healing well without discharge. Every second black silk suture was removed. There was slight separation of skin edges at the lower end of wound. This was coapted with two flamed "dumb-bell" adhesives and a dry gauze dressing. Pulse rate was 86 full and regular; blood pressure 92/64—left arm. Two days later the dressing was removed. The incision was clean and healing well. All remaining black silk sutures were removed and two additional "dumbell" adhesives placed. The patient completely recovered and was discharged to a private physician.

Radiographic examination made at the time of operation of the right-upper extremity, after visualization of the vessels with hippuran, showed the brachial artery and several of its branches in the region of the lower-most portion of the humerus and the radial and ulnar arteries with their branches. A distended portion of vein (brachial) overlying the lower end of the humerus was also noted.

The gross pathological description was as follows: Specimen consisted of a small piece of tissue, hard in consistency, and the appearance of and said to be a vein. Microscopically, the tissue was vein with marked proliferation of the intima with partly organized clot. *Diagnosis:* Chronic endophlebitis.

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# MULTIPLE PYOGENIC LIVER ABSCESSES*

## REPORT OF A CASE DUE TO BACILLUS PYOCYANEUS WITH RECOVERY

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BY multiple pyogenic liver abscesses we mean more than one simultaneous inflammatory process in the liver caused by a bacterium and continuing to suppuration. Parasytic abscesses are not included. Abscesses due to the gas forming organism do not form suppurative lesions. They are not a medical rarity, but are seen rather frequently in surgical practice and are more common than single pyogenic abscesses.[1] They are usually a sign of neglect or of too late an institution of adequate treatment.

### ETIOLOGY AND PATHOGENESIS

Multiple liver abscesses are always the result of spread of infection from a primary focus elsewhere in the body and are transported to the liver via the

I. Portal Vein
  *A.* Appendix
  *B.* Rectum
  *C.* Colon
II. Bile Ducts
  *A.* Gallbladder and ducts
  *B.* Small intestine (typhoid)
III. Systemic Circulation
  *A.* Spread from suppuration elsewhere via hepatic artery
IV. Trauma
  *A.* Penetrating injury with introduction of infection
  *B.* Contusion and degeneration of liver substance and infection
V. Lymphatic Spread
  *A.* Gallbladder
  *B.* Intestine
  *C.* Umbilicus
VI. Umbilicle Vein
  *A.* Umbilicle infection in newborn
VII. Spread of Contiguity
  *A.* Perforation of stomach, duodenum, and colon
  *B.* Perforation of gallbladder

Approximately 50 per cent of the cases are a result of acute appendicitis[3] and pylephlebitis. Infections and ulcerations of the colon and rectum are rarer causes of abscesses of the liver. Infection of the extra hepatic biliary system behind an obstruction in the common duct is the second[5] most common cause of multiple liver abscesses. Ascension through the common and hepatic ducts must not be overlooked in cases of abscesses due to the typhoid bacillus although typhoidal pyemia is probably the more common cause. Suppurative processes reaching the liver via the hepatic artery may arise from a carbuncle, osteomyelitis, bronchiectasis, heart or other focus of infection giving rise to a septicemia. Traumatic origin of liver abscess is not as common a cause as one would believe with the liver being one of the most commonly injured of all intra-abdominal organs. However, traumatic multiple abscesses probably rate third in order of frequency. The spread of infection to the liver from the gallbladder,[9] intestines or umbilicus is not rare. Infection of the umbilicus of the newborn with resultant liver abscesses is becoming a medical rarity and when found now is usually the result of the midwife or neglected baby and not an occurrence in a well regulated maternity hospital or ward. A perforation of the gallbladder, stomach or intestine with its contiguous location does not result in intrahepatic abscess formation unless it is a case of a

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missed diagnosis, or a silent condition, slow perforation, walling off and gradual spread by spilling of the contaminant.

The bacteriological cause of abscess may be many. Bacillus coli is the leading agent.[2] Hemolytic, non-hemolytic and viridans streptococci, albus, aureus and hemolytic staphylococci, pneumococci, Bacillus faecalis alcaligenes, Bacilles subtilis, diphtheroids, Bacillus protens, spirochetes,[6] Friedlander bacillus,[12] Bacillus pyocaneus have all been found as causative organisms.

## PATHOLOGY

The distribution of the pathological processes in the liver depends upon whether or not the infection is brought to the liver by means of the hepatic artery, portal vein or bile duct ascension. The abscesses are more pronounced around the bile ducts in cholangitis. The liver is grossly enlarged. The surface nodules or softened areas may be palpated. The edges are palpable and the color dark green or blue or tinged with a jaundic hue. On cut section, the areas of necrosis may be seen like bird shot and large varying in size, softened, filled with pus, the cavities containing ragged edges and perhaps bile stained pus, especially in the cholangenic abscesses.

The microscopic picture is typically one of necrosis with polymorphonucleur infiltration with pyogenic membrane formation being attempted, the intervening hepatic cells being the seat of cloudy swelling or toxic degeneration. The bile ducts may be dilated if obstructed and filled with bile stained pus.

## SIGNS AND SYMPTOMS

The signs and symptoms may be briefly tabulated as:

| Signs | Symptoms |
|---|---|
| Tenderness | Fever |
| Rigidity | Chills |
| Enlarged liver | Nausea |
| Palpable mass | Vomiting |
| Ascites | Pain |
| *X*-ray evidence | Dyspnea |
| Toxicity | Lassitude |
| Jaundice | Sweating |

## DIAGNOSIS

The presence of multiple liver abscesses may well be suspected in a patient who has appendicitis, or who has had an appendectomy and develops chills, fever and tenderness over the liver region, especially if the organ becomes palpable and the white count becomes elevated. Charcot's triad of fever, chills and jaundice in hepatobiliary disease points to cholangitis which if not relieved will go on to abscess formation in most cases. Nausea and vomiting may be suspected in practically all cases. Tenderness over the liver, muscle guarding or rigidity, palpable liver and right scapular pain are all localizing aids. With acute suppurative processes within the liver parenchyma a high leucocytosis is to be expected and should exceed 25,000 white blood count per cubic millimeter of blood, with a strong shift to the left, unless the patient is in a very poor condition. Dyspnea, extreme lassitude, and profuse sweating are associated findings. These patients are extremely sick, perhaps too weak to talk out loud. Ascites may develop in severe cases.

Thorium dioxide as an aid in diagnosis of these cases is not as important as it is in the diagnosis of solitary liver abscess. Three to four days are necessary for the best results[10] since the drug must be given intravenously daily for three days and is then phagocytized. Any ill effects of the radio-active drugs develop slowly and would appear later.

*X*-ray elevation of the right side of the diaphragm with or without basilar atelectasis or effusion is suggestive of subdiaphragmatic or intrahepatic mischief. The absence of primary lung disturbance and the restricted movements of the diaphragm aid in roentgen diagnosis. Deep abscesses, abscesses in the undersurface of the liver or the left lobe are less apt to produce these findings.

## TREATMENT

With a condition which is so often fatal, and which is shown statistically to have a

mortality rate of more than 95 per cent, treatment is a problem of prophylactic practice primarily. Perhaps an appendix may be removed that is not suppurative, perhaps a normal appendix may be removed; but rarely does death follow these uncomplicated procedures. The antiquated belief that surgery is for the gallbladders with stones only is to be abandoned. The constantly falling operative mortality, the newer anesthetics (for many people dread an operation because of "coming out of ether") will aid in allaying the patient's fear of operation. Keener diagnosis and more thought and thoroughness shown by physician and surgeon alike will aid in more sharp diagnosis and earlier operations for conditions causing these complications.

In active treatment, cardinal principles may be stated which apply in such a pathological state anywhere. Besides these there are special points of interest that should be mentioned, namely: (1) Proper preparation of patient; (2) treat primary site; (3) drain pus, if possible; (4) modern chemotherapy where possible; (5) Special means of treatment: (a) negative bladder pressure, (b) negative intraductal pressure.

*Proper Preparation and Nourishment.* In toxic liver conditions one of the most important functions to fail rapidly is glycogenesis[3] and hence the intravenous administration of glucose solution is of utmost importance, 100 to 400 Gm. being given per twenty-four hours. Mineral and fluid balance must be maintained by means of solutions of Hortmans, Ringers, lactate, or saline. With the liver function decreased the prothrombin time is frequently lengthened and vitamin K is necessary, especially if surgery is indicated. This may be given with bile salts if given orally, or given by hypodermic injection. Transfusions may be necessary if the patient presents a low red count, hemoglobin, or extreme toxicity.

*Treatment or the Primary Site of the Infection.* We have purposely not said the removal of the primary site for in most cases such prolonged and bothersome surgery is contraindicated. An appendiceal abscess is better drained and the appendix left in place than to disturb any pyogenic membrane or omental wall that may be forming. To remove a diseased gallbladder full of stones, the seat of an empyemia, or other inflammation may precede the signing of the death certificate. The removal of a large common duct stone which necessitates any length of time is better not done. Far better is it merely to drain the gallbladder with a tube left in the cystic duct, or merely to open the common duct, remove what stones present conveniently and place a T tube in position. When a patient can not live through these procedures, what chance has he with more insults?

A perforation in an adjoining viscus is naturally best closed if possible. Drainage of the abdomen is practically always indicated. Carbuncles are serious conditions and when a patient with a carbuncle develops multiple liver abscesses it is a sign of bacteremia and a fatal outcome can be predicted. However, cruciate incisions with copius glycerine packs or negative pressure cupping, we believe to be of more value than *x*-ray alone; a combination of these procedures with radiotherapy is probably the best. The wisdom of the use of *x*-rays and sulfa compounds together is still a debated subject.

*Drainage of Multiple Liver Abscesses.* This is feasible in practically only one instance, that is, when the suppurative processes result from cholangitis. Here the ducts can be drained and, indirectly, also the abscesses higher up, by means of cystic or common duct drainage with or without negative pressure.[17] Drainage of multiple abscesses originating in any other manner is inadequate. Negative intrabladder pressure will be discussed later. Surgical attack of these lesions is not practical and merely adds injury and insult to the already present condition.

*Modern Chemotherapy.* This together with the sulfa drugs may aid in the treatment of these conditions. Sulfanilamide

would be the drug of choice in streptococcal lesions. The cure of liver abscesses with sulfanilamide has been reported.[15] However, it appears that there are many loopholes in these reports, one case being diagnosed clinically and the other showing negative cultures. It is interesting to note that the sulfanilamide concentration in the bile reached 2.5 mg. per cent. In one case of Bacillus pyocyaneus liver abscesses sulfathiazole was used but no bile concentrations were determined. We believe that for routine use sulfathiazole or sulfadiazene is the drug of choice. In Friedlander's or pneumococcic infections sulfapyridine is probably the best agent.

We have a powerful weapon in these drugs, but like any other weapon, it must be used sufficiently to be of any aid defensively. These drugs should be used in large enough quantities to maintain adequate blood concentrations. Since stone formation takes place in the acid urine with acetyl formation, adequate alkalization is necessary. In many cases with excessive nausea or vomiting the soluble forms should be given intravenously. The rectal route of administration has nothing to recommend its use, unless no other method is possible.

*Special Means of Treatment.* Hendon[3] has described a method of producing negative pressure in the renal apparatus by producing a bladder suction. This, he states, caused an increased percentage of urinary output in relation to the fluid intake. We have never used this method and cannot speak with any authority about it.

The production of a negative pressure within the bile duct system is a method that is most commendable. Every surgeon knows the value of liver decompression in severe cases of stone with jaundice. The introduction of a cystic or common duct tube and the drainage of such with a negative pressure equal to that of a column of bile from the ducts to the bottle on the floor is one of the most important phases in liver decompression and especially cholangiogenic abscess drainage.

Dr. W. G. Benjamin[17] recommends the gradual decompression of the liver to prevent the parenchymal damage and hemorrhage associated with the sudden and total release of pressure from within the ducts. He fastens his tube in securely and then at intervals allows the bile to flow off and thus gradually reduces the intrahepatic positive pressure to a negative one. We have seen many cases of cholelithiasis with white bile due to extreme liver damage drain for several days, and then have the liver cells return sufficiently to secrete well pigmented bile and go ahead to complete recovery.

## PROGNOSIS

The mortality is high, being quoted by Ochsner[7] as 95 per cent in a series of twenty cases of multiple liver abscesses. In solitary abscesses, however, the mortality was 37.5 per cent in a series of twenty-four cases. Various other authors[1] have quoted the mortality rate at from 59 to 100 per cent in multiple liver abscesses, most statistics being over 95 per cent. The condition is met with as a complication of some other condition as will be noted, and when further complicated by spread into the thorax, pericardium, peritoneum or to other viscera, the prognosis is even more grave, recovery being extremely rare.

## COMPLICATIONS

Multiple pyogenic abscesses of the liver are never primary, but are complications of a pre-existing condition and when further complicated a fatal outlook can be forecast. Subdiaphragmatic abscess, empyemia, lung abscess, hydrothorax, pulmonary embolism, peritonitis, pericarditis, endocarditis, colon and stomach fistulas, brain abscess and amyloid disease,[2] all go to make the problem more widespread and fatal. All result either from direct or indirect spread of the infection except amyloid disease.

CASE REPORT

A search of the literature failed to reveal a proved case of multiple liver abscesses due to Bacillus pyocyaneus with recovery. A brief summary of such a case follows:

Mr. J. R., age sixty-five, was referred by Dr. H. J. McKeown, of the Medical Department. He was admitted to the hospital on November 14, 1941. There was a record of a previous hospital admission on February 22, 1940, for prostatic hypertrophy with mild uremia.

His chief complaints were abdominal pain, chills, and nausea for two weeks. He had had indigestion and colicky pains in the right upper quadrant for three years. Two weeks before admission he developed sharp colic and pain in the right upper quadrant accompanied by fever, chills, vomiting and sweating. This attack passed but he had numerous attacks essentially the same since then. He had clay colored stools intermittently, and developed a progressive jaundice since the first attack. He had gone down hill rapidly during the few days before admission.

He had undergone no surgery except cystoscopic work on February 22, 1940. A horse fell on the patient five years previously breaking his right arm and left leg. He never had any contagious or infectious disease.

Physical examination revealed the patient to be a thin, well developed man of sixty-five, who was jaundiced and appeared very weak and in distress. He talked with some effort. His head was normal except for a sebaceous cyst beneath the right eyebrow. The eyes were normal except for jaundiced sclerae and arcus senilis. Examination of the nose, throat, lungs and cardiovascular system showed nothing abnormal. His blood pressure was 110/65. The abdomen was puffy in appearance and markedly tender on the right side, chiefly just below the costal margin. There was splinting of the muscles on the right side. The liver, spleen and gallbladder were not palpable. The extremities showed nothing abnormal and the skin was moderately jaundiced. The axillary and inguinal glands were palpable but not tender. Rectal examination revealed a normal prostate.

Urinalysis showed the presence of bile. Bleeding time was four minutes, clotting time one minute, and prothrombin time twenty seconds (fifteen seconds equals normal). Hemoglobin was 11 Gm. There was slight hypochromia, anisocytosis and poikilocytosis. The red blood count was 3,420,000. The total white blood counts on graph showed a marked shift to the left. Kahn and Wassermann tests were negative, icteric index was 55 units, and the non-protein nitrogen was 32.4 mg. per cent.

The patient was prepared for surgery by intravenous administration of glucose, vitamin K, the oral administration of bile salts and a high carbohydrate diet. He was operated upon November 19, 1941, with a preoperative diagnosis of subacute cholecystitis, cholangitis and common duct obstruction with multiple liver abscesses.

Under local anesthesia the abdomen was entered through a high, right rectus incision. The gallbladder was delivered into the wound and found to be enlarged and very firm. There were plastic adhesions from the lower portion of the gallbladder to the neighboring duodenum and falciform ligament fat. The gallbladder was aspirated. It contained very dark bile. The lower portion of the bile of the gallbladder was very flocculant and semisolid in consistency. Numerous large, faceted stones were removed from the cystic duct where they had been impacted. The common duct was palpated and no stones or other pathological process was found. No other stones could be palpated. A large catheter was anchored into the gallbladder down to the cystic duct and irrigated with saline. Bile began to flow freely from the cholecystotomy tube. There were numerous small nodules in the liver substance that could be palpated. One of these was aspirated with a needle and contained pus, of which a culture was made. The cholecystotomy tube was brought out through a stab wound to the right of the incision. Due to the patient's condition no further surgery was attempted. The abdomen was closed in layers.

The postoperative diagnosis was subacute cholecystitis, cholelithiasis, common duct obstruction (due to edema of duct) and multiple liver abscesses.

The submitted tissue showed chronic cholecystitis with cholelithiasis and the culture from the aspirated liver abscess revealed Bacillus pyocyaneus. (Fig. 1.)

The postoperative course was uneventful. After the second postoperative day the patient's temperature stayed normal. From the fourth to the twelfth postoperative day he drained profuse green pus. Bile drained well

from the cholecystotomy tube from the day of operation and it was removed on the twelfth postoperative day when the icteric index was

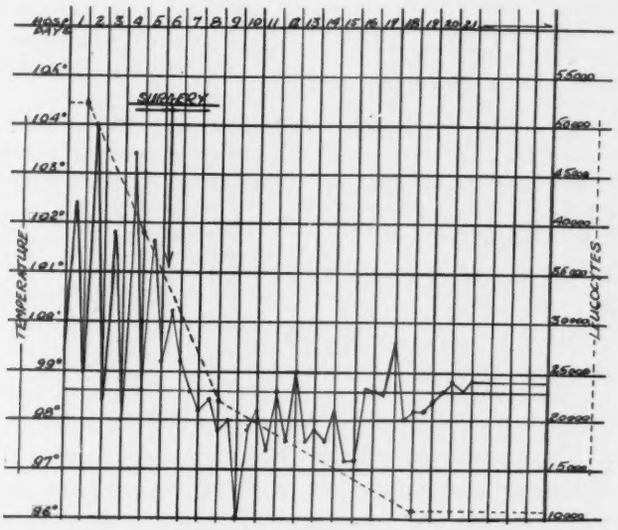


FIG. 1. Chart showing temperature and leucocyte count.

10.8 units. On the seventeenth postoperative day he was discharged in a wheelchair in a good condition.

He was seen again one month postoperatively and was in good enough condition to make the trip to his home seventy-five miles away. He was last seen three and one half months postoperatively and had no complaints. He had regained most of his strength.

## BACTERIOLOGY

The Bacillus pyocyaneus as the cause of blue-green pus was first demonstrated by Gessary in 1882.[18] It is a short, gram-negative rod. It may resemble the diphtheria bacillus because of granules it sometimes contains. It is an aerobe and a facultative anaerobe. However, it does not develop its characteristic pigmentation under anaerobic conditions. Hence, in our case the aspirated pus from the liver was milky color and the drainage brilliant green.

The Bacillus pyocyaneus is one of the less virulent pathogenic bacteria. However, cases of death due to infection with it have been reported. It is a frequent cause of epidemic umbilical infection in the newborn. Bacterolytic and leucocytic destroying ferments have been described by Wassermann and Gheorghiewski.[18]

## CONCLUSION

We believe this to be the first proven case of multiple liver abscesses due to Bacillus pyocyaneus, from which the organisms were cultured from the liver abscess, to progress to complete recovery. A brief outline of our method of treatment is given as well as a summary of the pertinent literature on the subject of multiple pyogenic liver abscesses.

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If Volkmann's ischemic contracture occurs it should be recognized in its early form and treated immediately by incising the fascia of the forearm in order to evacuate the underlying hematoma. Special splints should be fitted for gradual correction and stretching of contractures. In most instances radical operations are eventually necessary.

# PRIMARY BRONCHOGENIC CARCINOMA*

## REPORT OF A CASE

CAPTAIN CLARENCE C. HETZEL, JR., M.C. AND FIRST LIEUT. JAMES H. WALKER, M.C.
MCCHORD FIELD, WASHINGTON

THIS case of pulmonary carcinoma is reported for the following three reasons: (1) It illustrates the point that malignant tumors will be found in army hospitals because of the overlapping of the age of malignancy and the draft age limit; (2) it illustrates the adequate work-up that a patient can receive on entering an army hospital; and (3) this case presents several features not commonly seen as such in primary bronchogenic carcinoma.

### CASE REPORT

No 4798, a forty-year old white male, was admitted to the McChord Field Station Hospital with complaint of pain in his right chest. The family history was noncontributory. His past history revealed that the patient had an urethritis in 1937, an appendectomy and tonsillectomy in 1939, had worked in a state mental institution during the past year and was associated with tuberculous patients, and that he had been under the care of his private physician for an infarct of the right lung and possible tuberculosis.

The onset of the present illness dates back to 1937 with symptoms of pain in the right side of the chest and hemoptysis. In 1938, the patient was in a southern hospital twice because of these symptoms. He was bronchoscoped and had a bronchogram. Since no treatment was recommended, it is assumed that the examinations at that time were negative. The hemoptysis often came on suddenly and without warning, although it did seem to occur more often while exercising. At times the patient had a feeling of warmth in his chest and then he would cough blood. The hemoptysis was pure blood; at first it would be as much as one-half a cupful and during the next ten to fifteen days it would gradually decrease in amount and finally disappear for one to four weeks. There was always a dull nonradiating pain in the right chest, along the anterior costal margin and extending into the right axilla. During periods of active bleeding the pain would become sharp in character. The past four years the pain and hemoptysis have gradually become slightly worse. On admission the patient stated that he had not coughed blood for two weeks. He felt feverish and had a slight nonproductive cough. He had no symptoms of bronchial obstruction such as wheezing, dyspnea, or coughing foul-smelling sputum. There have been only about ten pounds of weight loss in the past four years. A review of the systems was otherwise noncontributory.

His temperature was 102.6°F., pulse 84, respirations 20, blood pressure 128/78, weight 136 pounds, height 66 inches.

A fairly well developed and well nourished darked skin male who did not appear very ill was admitted to the hospital. The patient had a moderate degree of scoliosis. The examination of the head and neck was negative. The patient indicated pain along the anterior costal margin which extended superiorly to the sixth interspace in the midclavicular line and laterally into the right axilla. There were a few moist râles heard in the right interscapular area of the chest, otherwise it was clear. The abdomen protruded moderately and a well healed lower right rectus scar was present. Rectal, neurological, bone and joint examinations were also negative.

Sputum examinations were negative for tuberculous bacilli, but always positive for blood. The tuberculin was negative to 1:1000 dilution after forty-eight hours. Gastric washings were negative for tuberculous bacilli. Sedimentation rates: 70, 46, 48, 48. Red blood cells numbered 4,484,000; hemoglobin 95; white blood cells 8,400; polymorphonuclears 70; lymphocytes 28, and monocytes 2. This count remained essentially the same during his hospital stay. Kahn and Wassermann tests

* From the Surgical and Medical Services, Station Hospital, McChord Field, Washington, Major Donald E. Reiner, Surgeon.

were negative, and the urinalysis was also negative.

*X*-rays revealed a mass of homogeneous

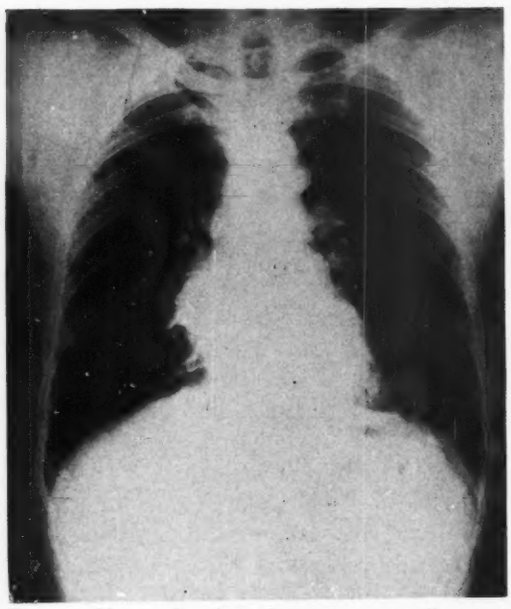

FIG. 1. *X*-ray showing the mass extending out from the right hilar region at the seventh interspace.

density, extending from the right hilar region at the seventh interspace about 1½ inches in diameter and of smooth outline. The mass did not cause any esophageal defect after a barium meal. A bronchogram revealed a slight puddling of the lipiodol just above the bronchus to the right middle lobe. Pyelograms and gastrointestinal studies were negative.

The patient's temperature returned to normal his second day in the hospital and remained within normal range during his stay in the hospital. On the second day he suddenly coughed about one-half a cupful of pure blood. During the next ten days this gradually decreased in amount so that on his twelfth hospital day he did not cough any blood. The bronchoscopist examined the patient, and his note is as follows: "Bronchoscopy revealed a smooth, rounded tumor mass just at the middle lobe bronchus which has no abraded surface, but began to bleed much and ooze up from the periphery and obscure a good view of the tumor. The carina was normally thin, moved normally with respirations and heart beat. No metastatic areas visible. I believe this is a benign tumor of the right main bronchus just proximal to the middle lobe bronchus on the medial wall." (C. C. Hetzel, Jr. Captain, M.C.) The consensus of opinion among the pathologists on the biopsy specimen obtained at bronchoscopy was a primary bronchogenic carcinoma, and probably of the small round cell type.

## REMARKS

The differential diagnosis involved in this case was between tuberculosis, a benign pulmonary tumor, and a primary malignant pulmonary tumor. Tuberculosis was ruled out by the absence of tuberculous bacilli in sputa and gastric washing examinations, negative tuberculin tests, and the *x*-ray picture was not indicative of tuberculosis. A diagnosis of a benign pulmonary tumor was made on the long duration of symptoms (four to five years) and their appearance before the age of forty, a loss of weight of only ten pounds in four years, and frank hemoptysis being one of the first symptoms to appear.[1,2,4] In addition to these points the bronchoscopic picture was that of a benign tumor.[1] Thus, when the biopsy report of a malignant pulmonary tumor was returned, the patient was re-examined carefully and laboratory data reviewed in order to rule out the possibility of the lesion's being a metastatic tumor. With such evidence as the only symptoms being pulmonary ones and the absence of positive findings in the rest of the body, the final impression at this hospital is that of a primary bronchogenic carcinoma.

Since this case presented several unusual clinical features, it was decided to report these, which are: (1) The long duration of symptoms (four to five years); (2) pain and frank hemoptysis were the earliest symptoms, instead of late as is the rule; (3) a loss of weight of only ten pounds in four years; and (4) the bronchoscopic picture was that of a benign tumor.

This patient was transferred to a large army general hospital for surgical treatment. "Patients with suspected or proved primary carcinoma of the lung are surgical problems until proved otherwise."[3]

## CONCLUSIONS

1. A case of primary bronchogenic carcinoma is presented.

2. Symptoms appeared early which are not usually seen until late in the course of the malignancy.

3. This case illustrates the thorough examination a patient may receive in a small army station hospital.

4. Malignancy will be found in members of the United States Army because of the overlapping of the draft age limit and the age at which malignant tumors are found.

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Fractures of the leg are accompanied by shock and cause extreme pain. With linear fractures the only signs may be swelling, ecchymosis and tenderness. With displacement the diagnosis is plainly evident by deformity, shortening, abnormal mobility, and crepitus.

The brief excerpts in this issue have been taken from "Fractures and Dislocations for Practitioners" by Edwin O. Geckeler (The Williams & Wilkins Company).

# Bookshelf Browsing

## THE DOCTOR, MEDICAL SCIENCE AND THE CLINIC*

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OUR country is at war and drastic changes have taken place in premedical and medical education. As a defense measure the government has introduced a new concept of medical education. After three years of an accelerated medical course the doctor will be permitted nine months in a hospital for a general rotating internship. His training under the accelerated plan has been continuous and progressive and some of the usual auxiliary features of a medical course have been abridged and many sharply curtailed. The graduation of a young doctor today is held under the shadow and repercussions of the world catastrophe of war. However, we may take renewed inspiration and new faith that no matter how difficult the road and how beset with trials and tribulations the medical profession shall not be wanting in co-operation or in that loyalty that it has so eminently donated throughout history.

New conditions demand new technics, but great moments in history have much in common. In 1861, our country was engaged in a gigantic fratricidal war to determine whether this union of the United States was to survive. The occasion was an address to the medical class at Harvard, on November 22, 1861, the speaker Oliver Wendell Holmes, Parkman Professor of anatomy and physiology. After eighty-two years Dr. Holmes could repeat: "The young man who has not heard the clarion voices of honor and of duty now sounding throughout the land will heed no word of mine. In the camp or the city, in the field or the hospital, under sheltering roof or half protecting canvas or open sky, shedding our own blood or stanching that of our wounded defenders, students or teachers—whatever our calling and our ability, we belong, not to ourselves, but to our imperiled country, whose danger is our calamity, whose ruin would be our enslavement, whose rescue shall be our earthly salvation. . . . You cannot all follow the armies of your country to the field. But remember that he who labors for the general good at home is an ununiformed soldier in the same holy cause with those who bear arms or minister at the side of the ambulance and in the camp hospital. Larrey claimed no precedence of Dupuytren, nor Guthrie of Sir Astley Cooper."

Society is composed of individuals and responds to evolutionary impulses in a manner similar to that of the organic world. Mere change is not necessarily progress. The medical undergraduate days, such as the writer knew, are changed and gone forever. Certainly the vista of the future is markedly different from that in June, 1909. The author is firmly convinced, however, that medical knowledge must be digested and that rest must precede and follow intense intellectual activity. During a student's medical course he receives an immense amount of instruction. The possession of medical knowledge is essential to his vocation. The rational organization of clinical and laboratory experience is the basis of his professional career. As time goes by, it becomes more evident

* Commencement address, Medical Department, University of Buffalo, March 24, 1943.

that in preparing to be a doctor he was dedicating himself to a life of scholarship. New medical alignments must be made from time to time. In general, his future education will be due to personally enforced discipline. There is in his case, first the professional or vocational education, and secondly the liberal education that concerns itself with the broad cultural background of mankind and its relation to the social order in which he is to live, to earn his livelihood and to function as a doctor. Doctors are the medical descendants of Ambroise Pare, John Hunter, Lister and Osler, as much as the product of the faculty. Their medical education up to graduation has provided only an introduction and a background.

The following is an example from the author's own experience: In June, 1909, a graduating class occupied the orchestra in the Teck Theater. After receiving his degree the doctor went his separate way. A period or epoch in his life was terminated. Yet all of us were committed to a medical career. We could not determine our professional environment but we could decide how we would react to that environment. Little did we realize what splendid discoveries in medicine were before us. In 1905, Schaudinn discovered the Treponema pallidum and the entire pathogenesis of syphilis was rewritten. Within a year Wassermann introduced his serum-diagnosis and in 1910 Ehrlich and Hata discovered salvarsan. Within the space of five years we were to witness the epoch making elucidation of a disease that wrecked human beings from the cradle to the grave and even unto the third and fourth generation. Looking forward Cushing was to describe dyspituitarism and Peyton Rous transmit sarcoma by a filterable virus, while at the same time Great Britain adopted compulsory Health Insurance. We were to learn that emetine was a specific for amebic dysentery and Shick was to demonstrate the susceptibility test for diphtheria. Morphine-scopalamine narcosis, under the euphemism of twilight sleep, was to bloom and fade. Aschoff was to elaborate the reticuloendothelial system, and Holst and Frolich postulate vitamin c; the Coolidge tube and the Potter-Bucky diaphragm were to enlarge the domain of roentgenology. During World War 1, Kendall was to discover thyroxin, Goldberger to envisage the cause of pellagra and Wagner von Jaurigg treat paresis by superinfection with malarial fever. The sedimentation test was on the way, and Rubins was to insufflate fallopian tubes for sterility. In 1921, Banting and Best isolated insulin and diabetes mellitus was to have a definite therapeutic remedy; the examination of the hollow viscera—cholecystography, ventriculography and urography—were to become important diagnostic aids while Minot and Murphy were to re-examine pernicious anemia and introduce raw liver diet. Collip was to isolate parathyroid hormone and its relation to calcium metabolism; and as a result tetany and certain bone conditions were to have a new interpretation and therapy. Shock and the treatment of burns were to have a rational explanation; blood banks and plasma therapy were established; biochemical deficiencies claimed a place in therapeutics, and the detection and clinical effects of the loss of water, electrolytes and plasma protein were to be developed. The mysterious and romantic subjects of the vitamins and endocrine that now adorn textbooks were to be crowned by the discovery and clinical application of the "sulfa" drugs. This recital of achievements in medical science since I was graduated, brief, as it necessarily must be, serves only to emphasize that medicine is an advancing science and demands continuous study and application.

On the other hand, the diseases we now know least about are high on the list of frequency, danger and disability. Cancer, hypertension, nephritis, cardiovascular disease and arthritis are at the present time our most dangerous in terms of mortality and morbidity. The commencement day orator thirty four years hence will no

doubt indicate to the graduating class of that day, the causal factor in arteriosclerosis, hypertension and arthritis. He perhaps will have much to say about the etiology of coronary thrombosis, cardiovascular disease and nephritis. He will consider if not explain the transformation of a disease entity into another type of malady, the refractory anemias and their analogue leukemia, the rôle of amino acids in human nutrition. He may review the specific isolation and therapy of the virus diseases. He will explain the cancer-producing substances that are known now to be present in vitamins, hormones and estrogens, as well as, in the coal tar product, anthracene. He may predicate or announce the etiology of cancer by discussing the peculiarities of biotin and its carcinogenic properties in relation to the vitamin B complex and a possible chemotherapuetic cure of cancer. The future expansion of chemotherapy will be noted and anticipated by the discovery of new chemical agents with clinical applications now so familiar in the sulfa drugs. There might well be a note of sadness when the future class day speaker looks back upon the social callousness of 1942 that accepted, without indignation, 93,000 deaths from accidents, of which 47,500 were workmen killed on or off the job.

It would appear that the doctor today must be a combination of a physiochemist and a laboratory technician. A short time ago the biochemical department at the Post-Graduate Hospital sent to the staff a short memo listing fourteen "new" tests for liver function—a Pandora's box of chemical gifts. I am not affected with kainophobia—a fear of new things—but frankly I sometimes wonder if we are not exhalting science at the cost of personal clinical capacity. My medical school days were spent in the brilliant twilight of the heroic age of medicine, the period of great clinicians with their splendid professional and cultural attainments. It was a period of close and friendly association, in the school, the clinic and in the wards. By personal contacts with the Masters we became recipients of their experience. We learned much of their medical intuition and clinical acumen. These are the clinical qualities of head, heart and hand that Stephen Paget in his delightful biography ascribed to Ambroise Paré. "Truly his theories and explanations are childish, and his ignorance of things not yet discovered is as profound as our own but put Ambroise on one side of the patient's bed, and a surgeon of our day, singlehanded on the other, and you will not find the balance of insight and practicality against Ambroise."

It would be interesting if one had the power of divination to cast another's horoscope, "to look into the seeds of time and say which grain will grow and which will not." However, it is possible to preview a young doctor's position in a wartime society as well as his prospective place in the postwar re-alignments of medical practice. The exigencies of war will limit his hospital experience to nine months after which time he becomes, automatically—if physically fit—a medical officer with the armed forces. His future, therefore, will be divided into three periods—unequal and wholly different—first the internship, secondly the war service and finally the postwar career. The nine months' internship is a war limitation, but it will start the young doctor's hospital training under the proper auspices. Furthermore, it will be the starting point for a real internship and residency when he is returned to civil life. It should be the duty of the medical schools and hospitals to assure all their staff officers, interns or residents, that their place, insofar as human predications can go, will be returned to them after the war. During the doctor's war service he will be able to appraise his talents better than today. Some will probably remain in active service—an honorable career offering great opportunities for distinction. Perhaps many have seen the series of paintings by Dean Cornwell entitled "Pioneers of American Medicine."* In two of the four

*John Wyeth and Brother, Inc., Philadelphia, Pa.

portraits the chief personage depicted wears an army uniform—Beaumont and Walter Reed. The talents of Paré, Hunter and Pirogoff differ only in their activation from those of Russell, Gorgas or Leonard Wood. The global war is advancing the frontiers of epidemiology and preventive medicine. World-wide malaria with new strains of the plasmodium and with new vectors, endemic plague in the coastal towns of North Africa, epidemic typhus and a new genera of hostile dysentery organisms now confront us. The war trained physician will be our main defense against these pathogenic armies of invasion. The Army trained doctor will become the leader in an expanding science of preventive medicine. The teaching of these army doctors in the postwar period will be a centrifugal force, spreading from our hospitals and medical schools to an enlarging sphere of usefulness. In addition the doctor with the armed forces will have a valuable experience in the psychology and character of men under the stress of unusual circumstances. It may also, if destiny is on his side, favor him with an exceptional training in one of the major subdivisions of medical practice. It is an interesting fact that about 20 per cent of the physicians listed in the Directory of the A.M.A. are full time specialists. Whereas over 70 per cent of the interns in the hospitals approved by the Council on Medical education and hospitals, have indicated their desire to qualify for one or other of the fifteen Specialty Boards. If we may judge the future by our experience in the past, we can foresee a definite trend toward postwar specialism and a remarkable acceleration in the resident system.

For example, in 1930, 338 hospitals had some 2,000 resident positions. In 1931, 518 hospitals had 4,556 residencies. Again, in 1934, there were 332 three-year residencies in approved hospitals. These 332 three-year residencies had increased to 1,791 by 1939, an increase in approved residencies of over 100 per cent per year. It should be understood clearly that a residency presupposes a period of training under direct teaching supervision and not just contact with patients. The residency should supply adequate clinical material for diagnosis and treatment, and at least one-sixth of the total period should be spent in the laboratory. There must be sufficient clinical opportunities for a thorough mastery of all the technical procedures in the operative specialties.

The primary function of a hospital is not that of a well managed hotel for sick people but that of a temple of medical science. Within the hospital the resident will acquire much additional training under supervision with added experience in diagnosis, treatment and clinical responsibility. Great as these increments to medical knowledge may be, they are not by themselves sufficient. Only from teaching or from association with a teaching group will the young doctor receive the stimulus so necessary for the full development of his talents. Allied to a teaching responsibility is the energizing effect of an independent adventure in either clinical or laboratory research. He need not be born a laboratory man in order to be identified with worth while research. The search for truth may be in the wards, the clinic, or in the amphitheater, as well as in the laboratory. Corrigan, Graves and Bright needed no laboratory to acquire medical immortality, while Lister could apply the laboratory discoveries of Pasteur, a chemist, to found modern surgery.

Some there are with sensitive imaginations who are "laboratory born" and who will be happy only in the pursuit of science. There may be one doctor with the divine vision to see through the fog of ignorance and with a flash of intuitive genius bring forth a scientific discovery that may be applied by others to the alleviation of suffering or cure, if not the banishment of some disease. However, it is significant that the science of Harvey, Hunter, Jenner, Koch, Lister and Banting was in no way imperiled because they were practitioners. In all probability a physician's investiga-

tive curiosity will not be productive research. That does not matter. He can, however, interest himself in the less common, or the obscure and unknown and thereby develop the joyful habit of continuously adding to his store of personally acquired medical knowledge. With less opportunity than now lies before the young doctor today, Paré could say: "See, how I learned to treat wounds made by gunshot, not out of books."

Medicine had its origin in service. It has maintained itself by adopting the discoveries in pure science. Its password should be competency; competency comes only with application and training. To know the trade name and dosage of one of the sulfa drugs is not a knowledge of pneumonia and "to dust" sodium sulfathiazole in an infected peritoneal cavity is not a training in the physiology, pathology or technology of abdominal surgery.

Medicine is not an isolated activity of society. It has no separate identity by and for itself. On the contrary, it is an integral part of the collective efforts of society. It is universal and ministers to all regardless of race or color or creed. Every doctor may say: "I am a man and nothing human is alien to me."

Stephen Paget draws attention to the creative function of the doctor. For example, let us consider an attending surgeon in charge of forty hospital beds. Allow him six weeks' holiday and put the average stay of his patients in the hospital at three weeks. That gives him 300 patients a year. Take any ten of these patients. Of the ten let us assume that one dies, one is none the better for treatment and three being cured of maladies which could not shorten life, gain nothing in length of days. That leaves five patients; of these five, let us guess that two gain five years, two gain ten years and one gains thirty years of life. That gives a gain of sixty years in ten cases, or 1,800 years on 300 cases. In twenty years, at that rate, the surgeon will have saved 1800 times 20, or 36,000 years of other peoples' lives. Of course, he cannot alone claim these extended years; many minds, hearts and hands are at work with him. Still, the years are saved.

In youth one is inclined to believe that life is a straight line; it is only a straight line when viewed in distant objectivity. It consists in the main of a series of hills and valleys, and only the mean trajectory is straight. There is in every life the effort, knowing or unknowing, to obtain a balance between the inner life and its external expression—a balance of work, of love, of play and of prayer. I know three "oldsters" now living beyond the biblical three score and ten—one in Buffalo and two in my own community. In their younger days they helped to weave the tapestry of medicine with all its splendid colors. If they had taken only a narrow professional view of life, their later days would be barren of the joy that comes to a fruitful and contemplative mind. They have as their reward the satisfaction that they once labored in the Master's vineyard. They now participate in the pageant of medical progress and review their youth at the meetings of the various medical societies and in the companionship of their junior colleagues. Their life represents a correct balance and they approach retirement as one who

> "Shall come to his grave in a full age,
> Like as a shock of corn cometh in,
> in his season."

If a physician's gaze is always fixed on his medical activities or if the focus of his viewpoint is its monetary reward, his vision will be truly myopic and he will miss the real significance of medicine as a way of life, as a balance of essentials. The physician should have a due and proper regard for the value of his services when expended upon those able to pay. It has been my experience that the remuneration from the practice of medicine is ordinarily quite sufficient for a reasonably comfortable life. You can never hope to be rich in the terms of the financial world from the practice of medicine. But I believe a doctor

will always have a sufficiency irrespective of the medical system under which he may practice. I cannot tell the name of any doctor, except for reasons of health, who gave an adequate medical service and suffered from a grave insufficiency of living income. However, I can name many physicians who embarked on an alien career of high finance called the "stock market" and who hoped to enrich themselves without labor and almost inevitably the end was disaster.

No one is complete unto himself. To be sociable with one's colleagues and competitors is to follow the tide of medical progress. In the society of his equals a young physician will derive the most pleasure but it is from men with superior talents that he will learn the most and have the greatest incentive to work and to develop himself. A valuable asset in his life is membership in his County and State Medical Societies as well as the American Medical Association. There is a tendency for the physician to lose touch with his medical society and to forego their meetings. These are the medical fora of his craft. It is only there that he will extend his experience and keep medically young by contact with youth. There he will learn of recent research and the contributions of his colleagues. From them he will receive the stimulus for further study. Their meetings will provide an intellectual domain where bright mind answers mind.

A young physician should cultivate his medical library and by familiarity learn how to utilize medical literature. By slow degrees and painful effort, by trial and failure he should acquire an ability to write easily and clearly. Writing even for an alert mind and facile pen require labor and training.

"Reading maketh a full man, conference a ready man and writing an exact man."

Remember that St. Luke was a physician and the best of the Gospels came from his pen.

Habits of scholarship when once attained will fill a doctor's life with interest. My personal inclination has been for biography; to read what other men, in other times, have made of their lives, how they have affected their environment or been molded by it, how in contributary service they have reached beyond their life age and influenced my life, as well as the lives of others. Medical biography is of outstanding importance in showing the development of medicine as well as society. To be familiar with the great medical men of the past is to understand the real significance of practice. To look at the second hand of one's watch is to recall Dr. John Floyer, the inventor, and meet his patient, Samuel Johnson; to cleanse one's hands surgically, is to see the pathetic figure of Semmelweis and realize the horrors of puerperal sepsis; to know Dr. Ephriam McDowell and Jane Todd Crawford, his patient, is to be present at the first ovariotomy in modern gynecology; and to study the career of Pasteur is to become acquainted with "the most perfect man who has ever entered the Kingdom of Science."

By daily study the mind can be developed into a trained mechanism. Any study will suffice if carried out day after day. The time spent at it need not be long. It is the daily repetitive application that trains the mind in concentration and memory. There is no better exercise than the acquisition of a reading and speaking knowledge of a foreign language. The acquiring of a second speech is an excellent method for cultural expansion. That is the real objective of education. It is a discipline, acquired by labor and the expenditure of time. It is, however, an end in itself, for mental discipline is based primarily on self-interest. Yesterday is past, and tomorrow is uncertain, but

"What each day needs that shalt thou ask
Each day will set its proper task."

A physician should be proud of his profession. It is an honorable calling, and one of the great intellectual disciplines. It has existed since the early days of man and has an authentic history, beginning four

hundred years before the Christian era. It has suffered much from war, revolution and politics, but, it has survived as an organized guild devoted to suffering humanity. Whether it is a profession or a trade it will survive as an organized unit of society. Always there is the individual doctor, and the individual patient—at birth, at illness and at death; and as that individual doctor advances with training and experience he will have greater and greater opportunities to minister to the welfare of mankind. The practice of medicine is a ministry.

"Blessed is he who carries within himself a God, an ideal, and who obeys it. Ideal of Art, Ideal of Science, Ideal of Country, Ideal of the Gospel Virtues. Therein lie the springs of great thoughts and great actions."

A recent social document (Beveridge) of world wide interest states: "In the presence of revolution we may require revolutionary solutions and not just a patching of our social structures." The social objective of a security and protection from the cradle to the grave will eventually be an economic and biological failure. The history of anthropology reveals no single instance of survival when the organism singly or as an individual member of a gregarious unit, failed to energize itself by personal effort in order to maintain and reproduce himself. If man is to survive as an individual social unit, free from the concentration camp of political slavery he must return to the ancient philosophy of the old Testament, "In the sweat of thy face shalt thou eat bread." This divine injunction was not given unto man as punishment but as a way of life, a rational program for happiness. Only those who work merit "A happy life and a happy calling." For centuries medical practice was in chains, enslaved by a rigid formalism which cared more for doctrine than for investigation. Great names dominated medical thought for centuries. Only with the emergence of the universal mind of a Leonardo did medicine become free and begin its remarkable progress. It would appear that the world at the present time is moving to the left. Today emphasis is placed upon quantity not quality. Research is ordered to pattern, while our cities grow larger and larger, and individuals live in more and more congested dwellings and "with the development of urban civilization and industry, physical deterioration becomes appallingly common and every sort of physical abnormality is increasingly prevalent."

Socialization of medicine is preached as part of a new Utopia with a vast bureaucracy (of mediocrity) for its administration. When the political state destroys the freedom of choice for a career, at that precise moment genius and initiative are also destroyed.

> "Between two worlds, one dead,
> The other powerless to be born."

A young physician looks out on a vast social revolution, global in range and viewpoint but national in application. Medical practice for better or for worse will change under the impact of revolutionary forces. He may be called upon to advise and treat the socio-political ills of his society in no less degree than in maintaining his own personal professional status.

> Fear not! life still
> Leaves human effort scope
> But, since life teems with ill,
> Nurse no extravagant hope;
> Because thou must not dream,
> thou needst not then despair.*

* Empodocles on Etna—Matthew Arnold.

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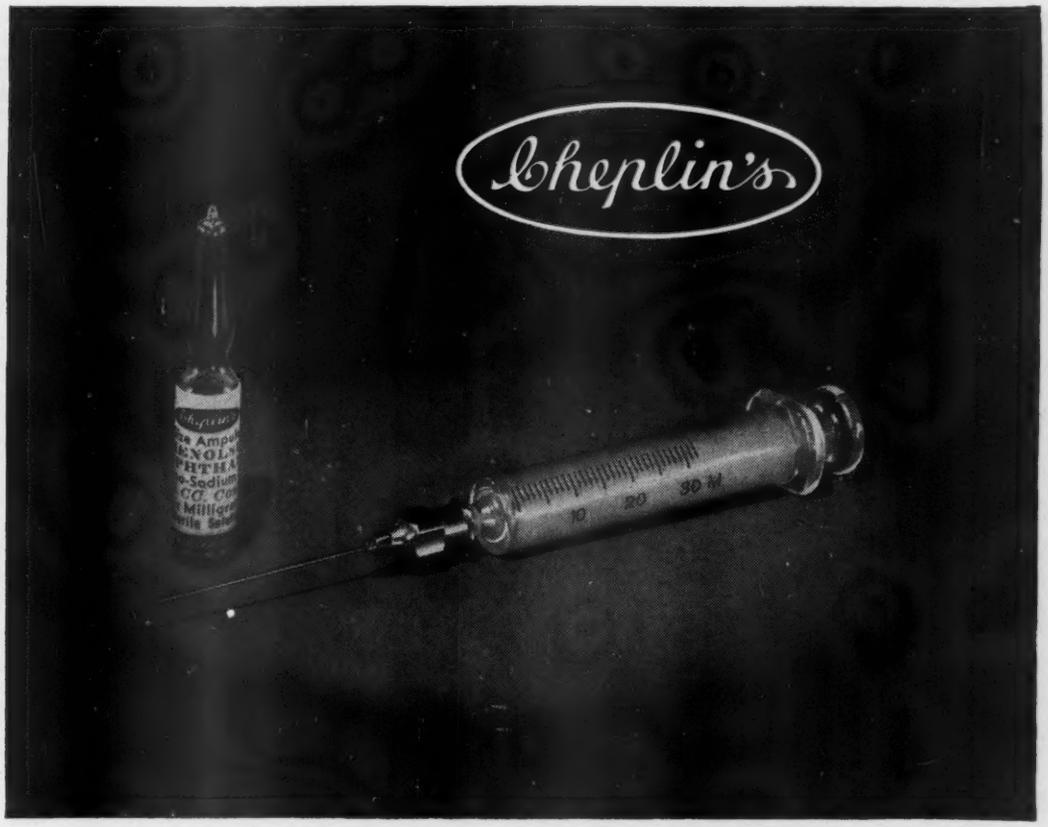


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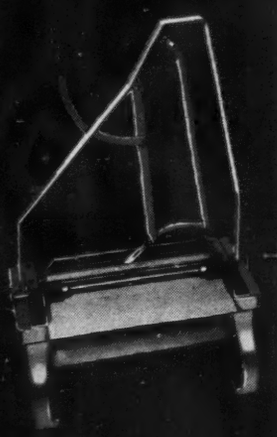

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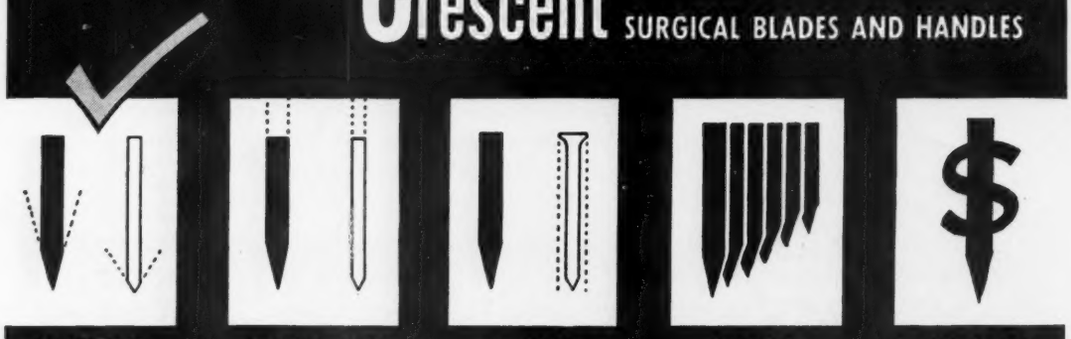

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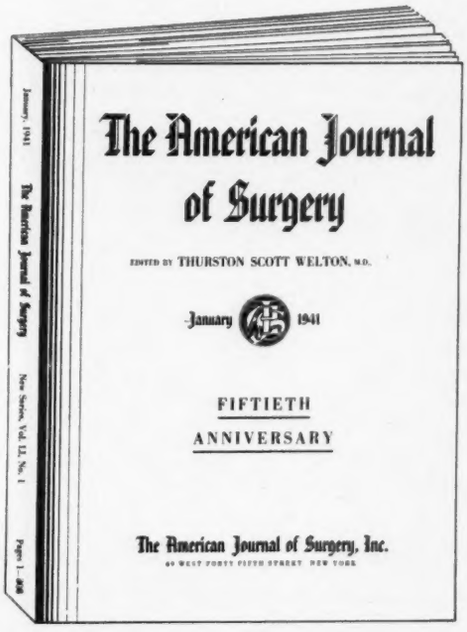


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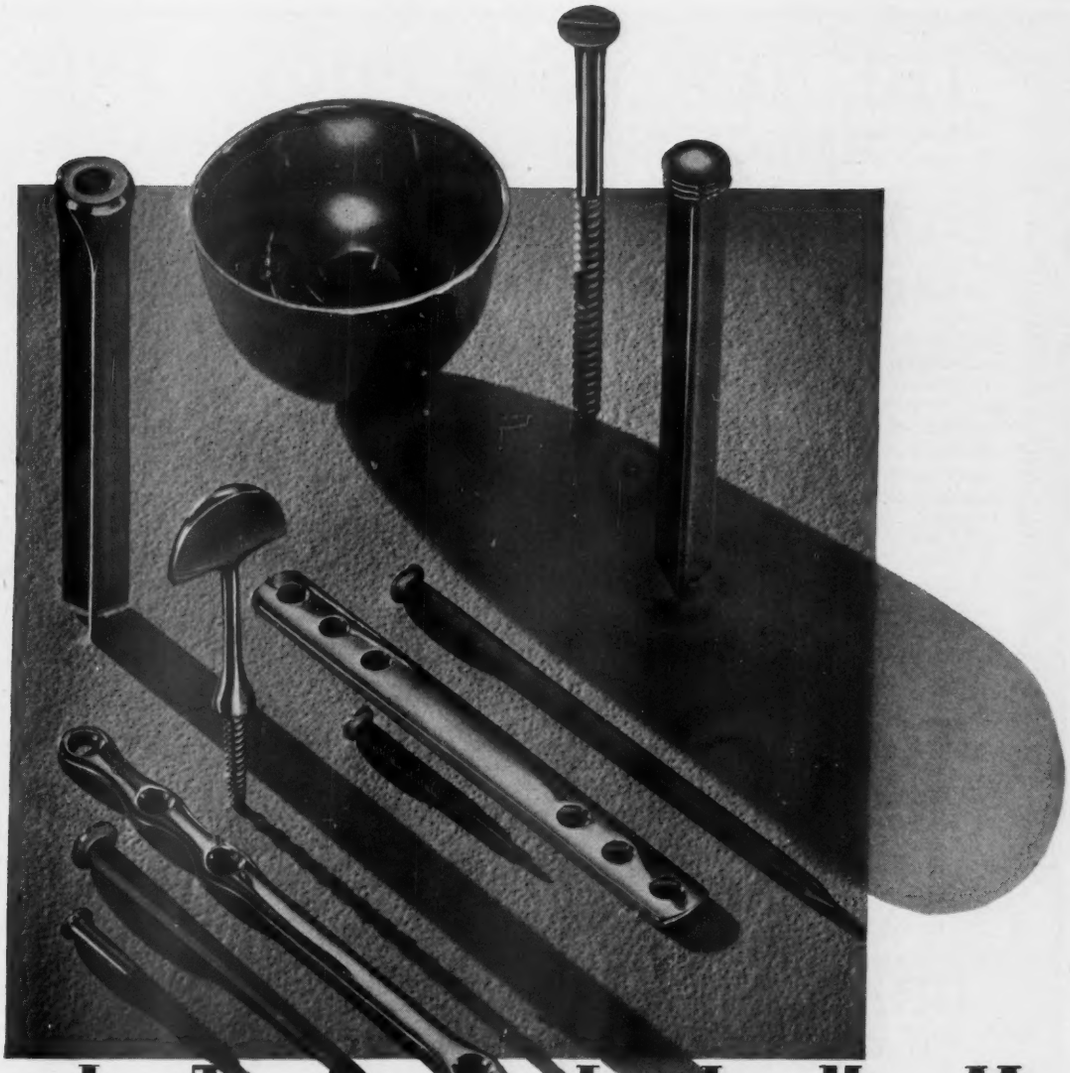

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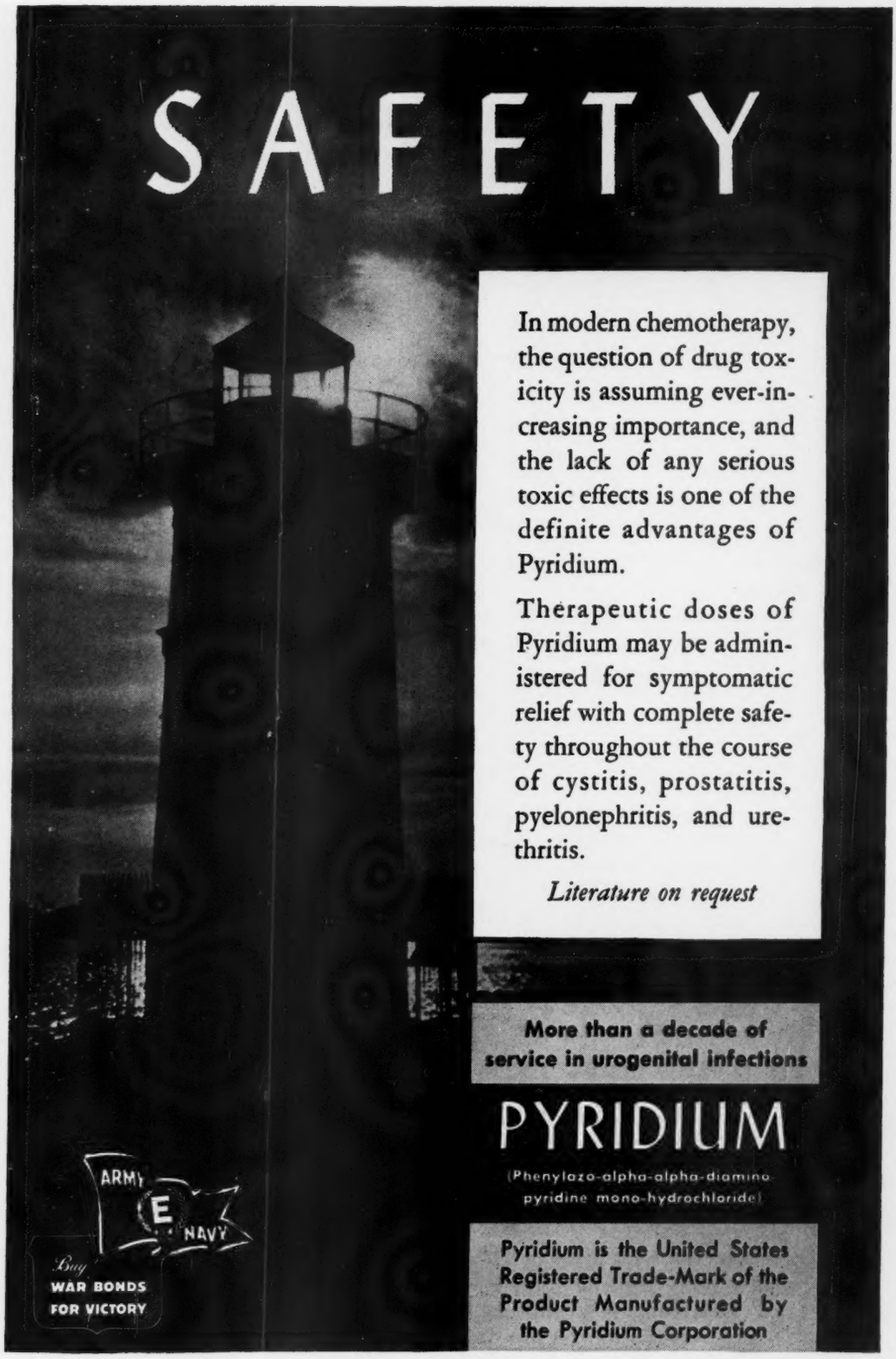
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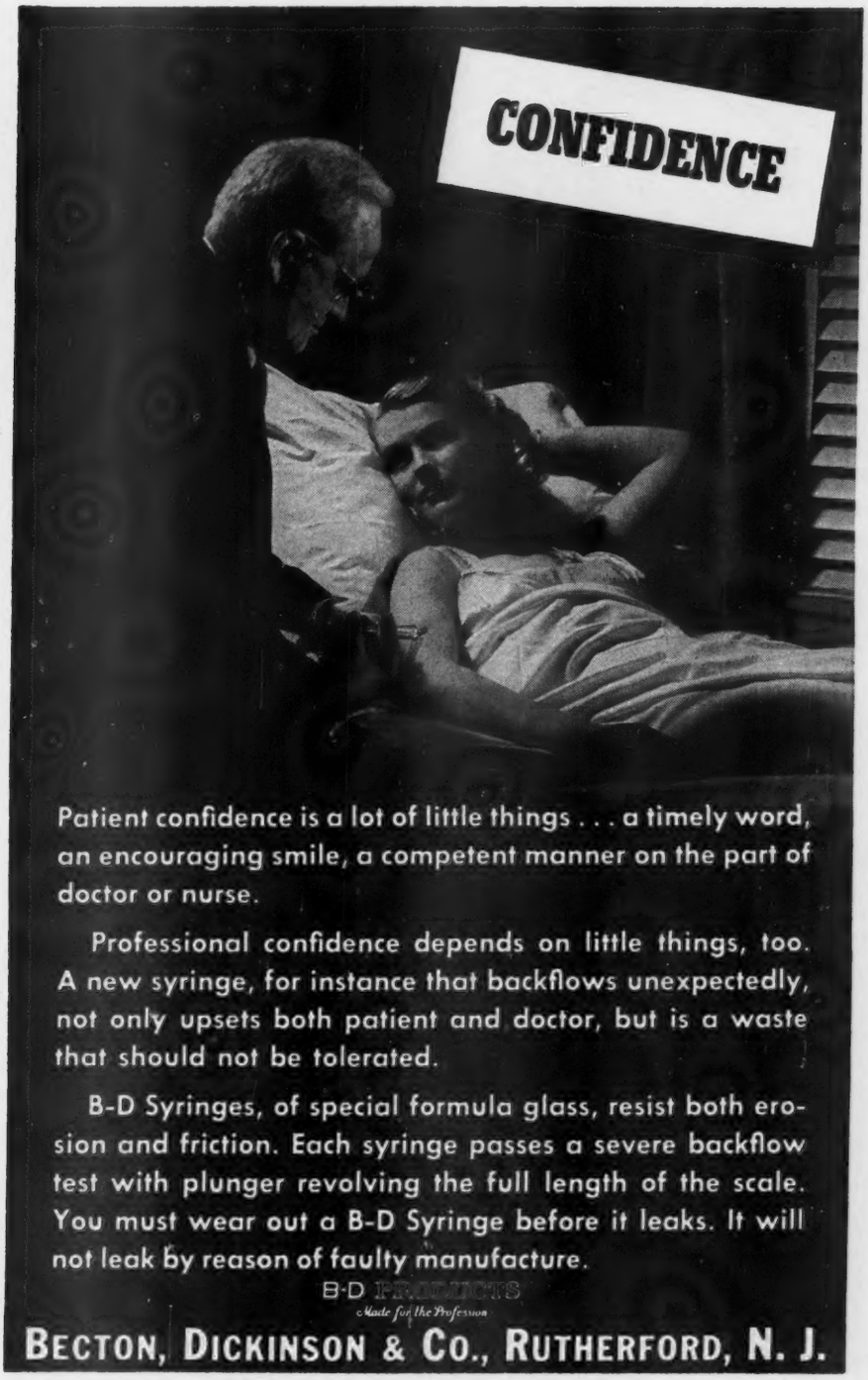
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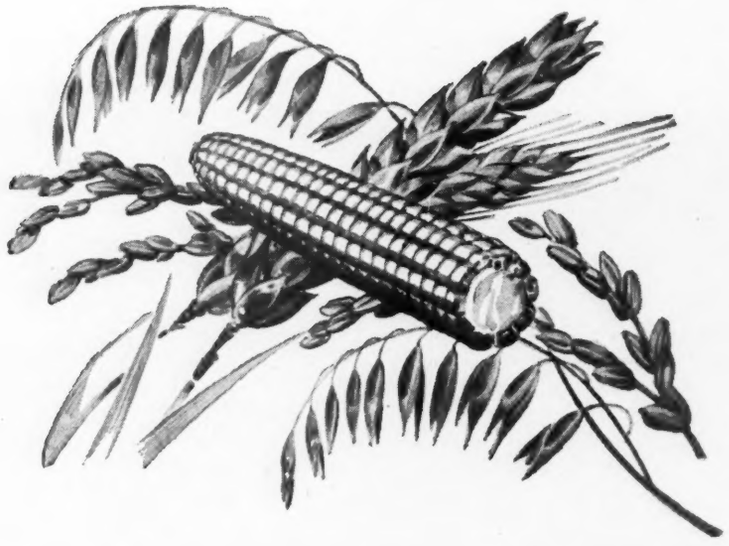

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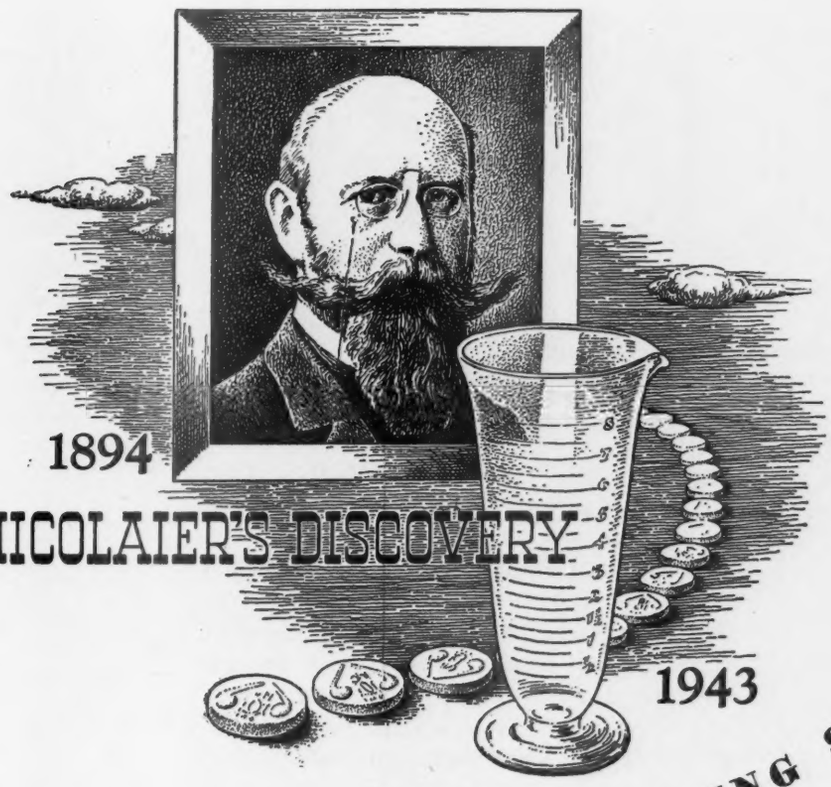


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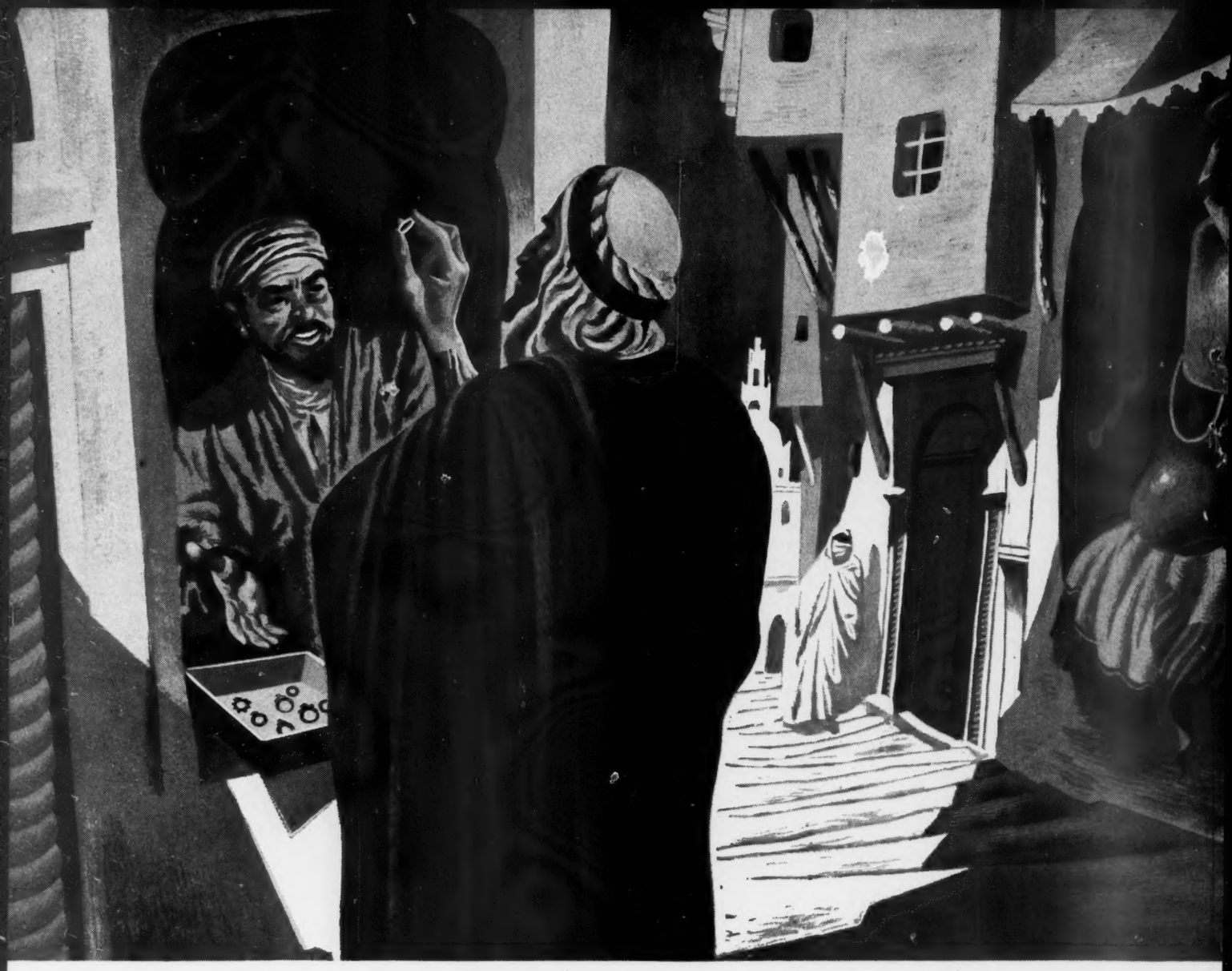

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